ADVANCED ELECTROCARDIOGRAPHIC PREDICTORS OF SUDDEN DEATH IN FAMILIAL DYSAUTONOMIA

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ABSTRACT

Objective. To identify accurate predictors for the risk of sudden death in patients with familial dysautonomia (FD).

Methods. Ten-minute resting high-fidelity 12-lead ECGs were obtained from 14 FD patients and 14 age/gender-matched healthy subjects. Multiple conventional and advanced ECG parameters were studied for their ability to predict sudden death in FD over a subsequent 4.5-year period, including multiple indices of linear and non-linear heart rate variability (HRV); QT variability; waveform complexity; high frequency QRS; and derived Frank-lead parameters.

Results. Four of the 14 FD patients died suddenly during the follow-up period, usually with concomitant pulmonary disorder. The presence of low vagally-mediated HRV was the ECG finding most predictive of sudden death. Concomitant left ventricular hypertrophy and other ECG abnormalities such as increased QTc and JTc intervals, spatial QRS-T angles, T-wave complexity, and QT variability were also present in FD patients, suggesting that structural heart disease is fairly common in FD.

Conclusion. Although excessive or unopposed cardiac vagal (relative to sympathetic) activity has been postulated as a contributor to sudden death in FD, the presence of low vagally-mediated HRV was "paradoxically" the best predictor of sudden death. However, we suggest that low vagally-mediated HRV be construed not as a direct *cause* of sudden death in FD, but rather as an *effect* of concurrent pathological processes, especially hypoxia due to pulmonary disorders and sleep apnea, that themselves increase the risk of sudden death in FD and simultaneously diminish HRV. We speculate that adenosine may play a role in sudden death in FD, *possibly independently of vagal activity*, and that adenosine inhibitors such as theophylline might therefore be useful as prophylaxis in this disorder.

Keywords: heart rate variability, bradycardia, signal averaged ECG, QT interval, QRS-T angle, T-wave morphology, hypoxia, adenosine, methylxanthines, theophylline, left ventricular hypertrophy.

INTRODUCTION

Familial dysautonomia (FD), or hereditary sensory and autonomic neuropathy type III, is a rare autosomal recessive disorder with extensive central and peripheral autonomic perturbations as well as small-fiber sensory dysfunction[1]. Most FD patients still die before the age of 50 and have cardiac autonomic dysfunction and an increased risk of sudden death believed to be mediated especially through respiratory failure and fatal bradyarrhyhmias[2-5]. Presently however, there are no sensitive and specific predictors to identify which patients with FD are at risk of sudden death. Although prolonged corrected QT (QTc) and JTc intervals can be life-threatening and have been described in 20-33% FD patients[6], ventricular arrhythmias (including *torsades de pointes*) have not been previously described in FD[5]. On the other hand, diminished cardiac sympathetic activity with relatively preserved or unopposed cardiac vagal activity has been hypothesized to be an important mediator of sudden death in FD[1,6,7]. Although low heart rate variability (HRV) is recognized for its ability to predict mortality or sudden death in other clinical conditions[8], low HRV might be expected to be a rather poor predictor for sudden death in FD if indeed vagally-mediated fluctuations (the major contributor to HRV[9]) are relatively preserved compared to sympathetically-mediated fluctuations in FD. In this study, we investigated the ability of several advanced ECG parameters, including advanced HRV, to predict sudden death in a small group of FD patients. Secondarily, we also investigated differences in these same parameters between FD patients and a group of age- and gender matched healthy control subjects. Although myocardial infarction and structural cardiac disease have occasionally been noted FD[3,10],

such conditions have not been electrocardiographically well-characterized in groups of FD patients. Our principal hypotheses were that one or more advanced ECG parameters would be accurate in predicting the occurrence of sudden death in FD patients over a 4.5-year follow up period, and that electrocardiographic evidence of structural heart disease would also be found in at least some FD patients.

METHODS

Patients. Ten-minute resting high-fidelity 12-lead ECGs were recorded in 14 FD patients (age range; 13-51 years; mean 25.3 ± 12.7 years) and in 14 age/gender-matched healthy subjects (age range; 14-42 years; mean 24.6 ± 8.0 years). Both groups consisted of six females and eight males. All FD patients were homozygous recessive for the common FD (*IKBKAP*) intron gene mutation and met clinical diagnostic criteria as they were of Ashkenazi Jewish extraction, lacked lingual fungiform papillae, did not have an axon flare after intradermal histamine, had decreased or absent deep tendon reflexes, and lacked overflow tears[11]. All control subjects were asymptomatic and had normal 12-lead electrocardiograms. Informed consent was obtained from all subjects prior to study. For subjects less than 21 years of age, signatures were obtained from both the participant and a parent.

Data collection. Data collection was approved by the Institutional Review Boards of the New York University Medical Center (New York, NY) and NASA's Johnson Space Center (Houston, TX). A PC-based ECG system with a frequency response to 300 Hz and a sampling rate of 1000 samples/s (CardioSoft Enhanced Cardiology, Houston, TX, or Cardiax, IMED Co Ltd, Budapest, Hungary) was used to simultaneously acquire the 12-lead conventional and advanced ECG data. Data collection for all FD patients took

place during a 1-week period in the spring of 2003. ECG data were collected until at least 256 beats were accepted for signal averaging and for variability analyses, as outlined below. Eleven of the FD patients also had echocardiographic results available based on incidental studies that had been (or were later) conducted for clinical purposes.

Analysis of ECG signals.

A. Conventional ECG parameters. Signals from the conventional ECG were analyzed automatically in software with respect to the heart rate, the PR, QRS, QT/QTc and JT/JTc intervals (Bazett-corrected), the frontal plane QRS and T-wave axes, and the presence of left ventricular hypertrophy by either the Cornell or Sokolow-Lyon criteria[12]. In addition, Anderson et al's subset of Sylvester's criteria[13] was applied to determine, in an objective fashion, the presence on the conventional ECG of a prior myocardial infarction.

B. Advanced ECG parameters derived from signal averaging. Signal averaging was performed using software developed by the authors at NASA's Johnson Space Center[14,15] in order to generate results for all of the following advanced ECG techniques: *1*) 12-lead High Frequency (HF) QRS ECG[14]; *2*) Frank-lead ECG parameters (derived from the 12-lead ECG using the reconstruction technique of Kors et al[16]), including late potentials-related parameters[17] and several other parameters related to the "spatial" ("3-dimensional") ECG (see below); and *3*) several parameters of waveform complexity (P, QRS and T) derived from singular value decomposition (SVD)[18] plus signal averaging[15].

In brief, the software automatically aligned the first ten 97% cross-correlated waveforms using their respective R-wave fiducial synchronization points, creating initial P, QRS and T wave signal-averaged templates for each channel. The software then

added subsequent incoming beats to the signal averages only when the cross correlations between the incoming beats and the existing templates in each channel were > 97%[14,15]. If in any channel the cross correlation between the template beat and the new incoming beat was less than 97%, then the software rejected the beat for all channels. For HF QRS, the conventional R-wave onset and the S wave offset were applied to the HF QRS signals in software at the same time as bandpass filtering for isolation of only those QRS frequencies between 150 and 250 Hz[14]. For the derived Frank-lead parameters, and for parameters of waveform complexity by SVD, the given wave within each channel was first referenced to the first 50 ms of the isoelectric T-P segment within that channel in order to eliminate any DC offset[15].

The following 12-lead HF QRS parameters were obtained at the end of signal averaged recordings: the total number of reduced amplitude zones (RAZ) present of the Abboud, Abboud-Percent and NASA types[14,19]; the overall "RAZ Score" for the given 12-lead HF QRS ECG[20]; the sum of the HF QRS kurtosis values[19] over the 12-leads; and the sum of the HF QRS root mean square (RMS) voltage values over the 12 leads ("RMS sum")[21]. HF QRS analyses were automatically performed in software for both the "CR" and the "V" precordial lead configurations[14,19] and the highest (RAZ parameters) or lowest (kurtosis sum; RMS sum) overall value from the CR versus V precordial lead comparison was then automatically chosen for final HF QRS-related outputs.

The following parameters were also obtained from the derived Frank leads at the end of signal averaging: the spatial P wave duration and the mean spatial velocity of both the P wave[22] and the QRS wave; the spatial mean[23,24] and spatial maximum[25] QRS-T angles; the spatial ventricular gradient, including its individual components (i.e., spatial

mean QRS and T waves)[23]; the spatial ventricular activation time (VAT)[26]; and the so-called "late potentials" parameters, including the filtered QRS duration (fQRSd), the RMS voltage of the terminal 40 ms of the filtered QRS complex (RMS40), and the duration of low amplitude (<40 uV) signal in the terminal filtered QRS complex (LAS40); i.e., after digital filtering between 40-250 Hz[17].

Finally, the following additional parameters of P, QRS and T waveform complexity were also obtained after signal averaging and SVD:

1) The complexity ratio (CR) of the given waveform (also known as principal component analysis ratio), which is the ratio of the second to the first eigenvalue[27,28] of the given waveform, multiplied by 100, i.e.,

$$CR = 100 \times \rho_2 \Big/ \rho_1$$

2) The relative "waveform residuum" (rWR) of the given waveform, which is the sum of the squares of the last 5 eigenvalues (or "non dipolar" components) of the given waveform divided by the sum of the squares of all eight eigenvalues[18,29] of the given waveform, multiplied by 100, i.e., $rWR = 100 \times \sum_{i=4}^{8} \rho_i^2 \Big/ \sum_{i=1}^{8} \rho_i^2$ where $\rho_1 \geq \rho_2 \geq \cdots \geq \rho_8$;

3) The *modified* relative waveform residuum (mrWR) of the given waveform, which is the ratio of the sum of the squares of the *third* through the eighth eigenvalues of the given waveform to the sum of the squares of all eight eigenvalues of the given waveform, multiplied by 100, i.e., $mrWR = 100 \times \sum_{i=3}^{8} \rho_i^2 \Big/ \sum_{i=1}^{8} \rho_i^2$ where $\rho_1 \geq \rho_2 \geq \cdots \geq \rho_8$; and

4) The "normalized 3-dimensional volume" (nV) of the given waveform, which is the product of the second and third eigenvalues of the given waveform divided by the square

of the first eigenvalue of the given waveform, multipled by 100, i.e., $nV = 100 \times \left[\rho_2 \times \rho_3 \Big/ \rho_1^2 \right]$

The mrWR and nV parameters are new parameters of waveform complexity introduced herein. These new parameters particularly emphasize the contribution of the third eigenvalue in the numerator, thus making them distinct from better known CR and rWR parameters, which instead particularly emphasize the contribution of the second and fourth eigenvalues in the numerator, respectively. The rationale for the use of these new parameters relates to the fact that in nearly all healthy individuals studied thus far at NASA, the most relevant T-wave amplitudes are actually contained not in the first three eigenvectors (or in the "dipolar components"[18,29]), but rather only in the first two eigenvectors (unpublished data). Thus, when disease occurs and the T-wave eigenvector energies start shifting into more downstream eigenvector components, these new indices are often more sensitive than the older indices, suggesting that in disease, T-wave energies may often be shifting not from eigenvector 3 into the even more downstream eigenvectors, but rather from eigenvector 2 (and/or from eigenvector 1 and 2) into eigenvector 3.

C. Advanced ECG parameters derived from variability analyses. Time series (~256 beats) for the RR and QT intervals were analyzed according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Clinical Electrophysiology[8]. For QT interval variability, besides using all of the standard leads, the first eigenvector and other "virtual leads" derived from SVD were also constructed and used in separate sets of analyses, inasmuch as these SVD-derived leads are less prone to noise and to other methodological artifacts

than is any standard lead QT signal, including lead II[30]. Specific variability analyses included: *1*) the standard deviation of normal-to-normal RR and QT intervals (SDNN RR and SDNN QT, respectively); *2*) the root mean square of the successive interval difference of normal-to-normal RR and QT intervals (rMSSD RR and RMSSD QT, respectively); *3*) the QT variability index (QTVI)[31]; and *4*) several other time and frequency domain indices of the RR interval variability, including (see[8]): Triangular Indices (TI and TINN) from the 256-beat RR interval histogram; the percent of adjacent normal-to-normal RR intervals more than 50 ms apart (pNN50); and the very low (0.0-0.04 Hz), low (0.04-0.15 Hz), high (0.15-0.40 Hz), and total (0.0-0.40 Hz) frequency powers of RR interval variability in natural log-transformed units (ln ms^2/Hz) calculated using the Lomb periodogram[32] method, and lastly, *4*) "non-linear" HRV including alpha 1 and alpha 2 (from detrended fluctuation analyses)[33] and the first and second standard deviations (SD1 and SD2) as well as the cardiac interbeat autocorrelation coefficient of RR intervals (rRR) from the ~256-beat Poincaré plot[34,35].

Statistical Methods.

Differences in parameters between groups were studied using nominal logistic regression and chi-square tests, with natural log transformation for all non-normally distributed data. In addition, sensitivity and specificity information was generated for all studied parameters and further characterized through construction and analysis of receiver operating characteristic (ROC) curves. All statistical analyses, including relative risk and survival analyses in relation to ECG findings in the FD group, were performed using SAS JMP software version 7.0 (Cary, NC). Differences between groups were considered significant at $P < 0.05$.

RESULTS

After 4.5 years of follow-up, four of the 14 FD patients have experienced sudden death. Patient 11, a 51-year old female, died within a few weeks of data collection due to respiratory arrest in the context of pneumonia and hypoxic encephalopathy. Patient 12, a 16-year old male, died of a night-time cardiorespiratory arrest 6 months after data collection. He also had pneumonia at the time. Patient 13, a 25-year old female, had a syncopal episode in the bathroom two years after data collection which led to hypoxic encephalopathy, coma and subsequent death. Patient 4, a 20-year old male, suffered from chronic and progressive lung disease and was using a ventilator during physical rehabilitation slightly more than four years after data collection when he experienced pulseless cardiac arrest, presumptive asystole and sudden death.

The advanced ECG parameters that most accurately predicted sudden death in the FD patients were the vagally-mediated HRV parameters, specifically the rMSSD, HF power, pNN50 and Poincaré SD1 of HRV. Patients 11, 12 and 13 all had especially low rMSSD HRV values at the time of data collection in 2003, whereas patient 4's value fell closer to average for FDs at that time (Figure 1). A survival analysis with reference to the level of HRV rMSSD in FD patients at the time of the index data collection is shown in Figure 2. The single best electrocardiographic predictor of sudden death in FD in this study was an rMSSD value less than 14 ms, which conferred a relative risk of 7.5.

Summarized results for all advanced ECG parameters for the FD patients versus the age- and gender-matched healthy controls are shown in the Table. The ECG parameters that best separated the FD patients from the healthy controls were the P-wave

and QRS-wave mean spatial velocities, as well as the alpha 2 index of HRV. However, there were significant differences between groups with respect to numerous parameters, including with respect to several different indices of HRV (especially the vagally-mediated indices as noted), several voltage-related parameters, and several repolarization-related parameters (i.e., parameters of beat-to-beat QT variability, T-wave morphology, and the QTc and JTc intervals). Seven of the 14 FD patients (50%, patients 4, 6, 8-10, 12, 14) were electrocardiographically positive for LVH according to either the Cornell or Sokolow-Lyon voltage criteria[12], two of these patients (4, 11) dying during the study. Echocardiograms were incidentally performed (for clinical purposes) in 11 of the 14 FD patients, six of whom had evidence of LVH (patients 4, 5, 6, 7, 10, 14). A total of 3 of the 14 FD patients (patients 4, 12, 14) had conventional ECG evidence for a prior MI on the basis of Anderson's subset of Selvester's criteria. Two of these patients (4, 12) later experienced sudden death.

DISCUSSION

The most important results from this study were that, first, diminished vagally-mediated HRV is especially predictive of the propensity for sudden death in FD patients, and second, that FD patients have multiple conventional and advanced electocardiographic abnormalities (compared to age- and gender-matched healthy controls) that tend to suggest structural heart disease, occasionally prior MI, but especially LVH.

Diminished vagally-mediated HRV and sudden death in FD. The finding that diminished vagally-mediated HRV is predictive of sudden death in FD might be

construed as paradoxical, at least *prima facie*, given that excessive or unopposed vagal activity (in relation to sympathetic activity) has often been implicated as a possible *mechanism of death* in FD, for example through induction of bradyarrhythmias or asystole, especially during sleep[1,6,7]. We believe that this apparent paradox can be resolved by perceiving the reduced vagally-mediated HRV not as a direct *cause* of sudden deaths, but rather as an *effect* of a concurrent pathological process that itself increases the risk of sudden death in FD while at the same time diminishing vagally-mediated HRV. That concurrent pathological process is *hypoxia*, and its presence is at least indirectly reflected in the fact that three of the four FD patients who had sudden death in this study were suffering from either acute or chronic pulmonary disorders at the time of their deaths. Hypoxia occurring as a result of sleep apnea is well known to reduce even daytime HRV, especially those parameters of HRV that are vagally mediated, regardless of whether the apnea is of the obstructive or central type[36-38].

This therefore shifts our attention to the role of concomitant hypoxia and pulmonary involvement in the outcomes of patients with FD. Death from pulmonary complications is the leading cause of death in FD,[2,3] although sudden death is a frequent cause of death, with most sudden deaths occurring at night[3]. In one study examining sleep recordings in FD, all FD patients demonstrated breathing disorders (especially central apnea) during sleep and 77% had more than 50 apneic spells per night[39]. In addition, FD patients are known to be especially susceptible to bradycardia and hypotension during chemoreflex stimulation associated with periods of apnea and hypoxia[40]. This is presumably due (at least in part) to deficient baroreflex-mediated attenuation of apnea-induced bradycardia[41] in FD patients, baroreflex deficiency being well characterized in

FD[42]. In healthy individuals, hypoxia and chemoreflex activation during apnea or hypoventilation generally leads to coactivation of vagal and sympathetic pathways[41,43]. Simultaneous vagal and sympathetic activation during apnea may help prevent heart rate from becoming excessively high, thus ensuring sufficient diastolic filling and cardiac output[43] without undue increases in myocardial oxygen demand. In FD patients, efferent vagal and sympathetic pathways are often both deficient, as is the baroreflex response[40,42]. This combination of abnormalities, along with the lack of an appropriate tachypnea response to hypoxia and inappropriate posthyperventilatory apnea in FD, appears responsible in some way for the central respiratory depression that occurs in response to even moderate levels of hypoxia[40]. Particularly in the context of some other condition in FD that commonly exacerbates hypoxia, such as aspiration pneumonia, restrictive pulmonary problems due to scoliosis, anemia, sleep apnea, etc[4], this central respiratory depression may abet yet more hypoxia and eventually result in life-threatening hypotension or bradyarrhythmia or at worst respiratory or cardiac arrest[40]. The question remains, however, 'through what mechanism precisely'?

Although it has not been previously addressed in the FD literature (to our knowledge), the release of adenosine by hypoxic tissues makes a major contribution to the decreases in respiration and heart rate that occur during systemic hypoxemia[44-48]. Adenosine has pronounced depressant effects on cardiac pacemakers[49], and at least in animals, the occurrence of bradyarrhythmia during hypoxia may be independent of vagal tone and driven by endogenous adenosine release[47,48]. Adenosine accumulation has also been implicated in the pathogenesis of vasovagal syncope[50], a condition commonly experienced in FD[42], and in bronchoconstriction[51]. Perhaps most importantly, adenosine

accumulation in the brain is also known to be associated with prolonged respiratory depression[44,45]. It is therefore tempting to speculate that therapeutic strategies that focus on attenuating adenosine-induced bradyarrhythmia and respiratory inhibition may be beneficial in helping to prevent sudden death in FD.

Methylxanthines such as aminophylline and theophylline are competitive antagonists to adenosine. Theophylline rapidly resolves the central respiratory depression associated with adenosine and in cats can completely prevent an otherwise long-lasting adenosine-associated respiratory depression when given prior to exposure to hypoxia[44,45]. Methylxanthines have also been shown to significantly increase HRV, particularly in the HF ("vagally-mediated") band and to normalize autonomic function in premature neonates[52]. This autonomic normalization might also be exemplified by theophyilline's role in the treatment of neurocardiogenic syncope[53,54]. Moreover, theophylline therapy has been shown to significantly reduce apneic episodes and improve arterial oxygen saturation in patients with central sleep apnea[55]. Finally, aminophylline therapy is often successful in reversing not only atropine-resistant AV block during inferior myocardial infarction[56], but also, importantly, bradyasystolic cardiac arrest that is resistant to both atropine and epinephrine[57,58]. While theophylline can increase gastro-esophageal reflux[59], a common problem in FD[60,61], the fact that a substantial portion of FD patients are now undergoing fundoplication and gastrostomy procedures[60,61] might make theophylline a tolerable therapeutic option in many patients. Pending controlled trials designed to test theophylline's efficacy in FD, the drug might certainly complement other measures that are presently used to prevent or ameliorate the effects of hypoxemia,

such as oxygen therapy itself and CPAP[4], especially in FD patients who may be at increased risk for sudden death as indicated by low levels of vagally-mediated HRV.

Although pacemaker implantation in FD patients may reduce the incidence of fatal bradyarrhythmia and syncope[5,62], it nevertheless does not entirely eliminate these conditions, and some FD patients with implanted pacemakers have still experienced cardiac arrest[5]. Thus, pacemaker placement alone may not be sufficient to prevent sudden death in all cases. Gold-von Simson et al.[5] have attributed the lack of complete success with pacemakers to the possible overriding effects of hypoxia and central respiratory depression. Assuming that ventricular arrhythmias are not the cause of death in these recalcitrant cases[5] (if so, then pacemaker-defibrillators would be indicated), it is possible that the inability to prevent fatal bradyarrhythmia in some pacemaker-resistant cases relates to the overriding depressant effects of adenosine accumulation – an hypothesis that remains to be investigated.

Changes in other ECG parameters. Although they were not as predictive of sudden death in FD as the vagally-mediated HRV parameters, the ECG parameters that best separated the FD patients from the healthy controls were the P- and QRS-wave mean spatial velocities, as well as the alpha 2 index of HRV. The P- and QRS-wave spatial velocities are measures of the rate of change of the size of the respective signal[22] and likely relate to conduction velocity. Therefore, the enhancement of these spatial velocities would be consistent with a relative diminution in efferent vagal activity in FD, given that cardiac vagal activity is known to diminish conduction velocity (i.e., has negative dromotropic effects)[63]. The relative diminution of efferent cardiac vagal activity in FD is also of course reflected in the decreased vagally-mediated HRV parameters

themselves (including decreased SD1/SD2 ratios on the Poincaré plot), and also with the *increased* resting heart rates, LF/HF ratios, values of alpha 1 and 2 (alpha 1 values typically paralleling those in the LF/HF ratio[64]), and the Poincaré plot interbeat autocorrelation coefficients (rRR)[35] in FD patients.

As noted, half of the FD patients were electrocardiographically positive for LVH by either Cornell or Sokolow-Lyon voltage criteria. These findings are also consistent with the overall larger electrocardiographic voltages found in the FD patients, as well as with the increased spatial QRS-T angles (which may reflect ventricular enlargement[23,26]) found in the FD group compared to the healthy controls. These are important findings given that LVH (and increased spatial QRS-T angle[24]) is by itself a significant risk factor for cardiovascular and total mortality[65,66], and that the propensity for sudden death also increases with the *degree* of LVH in other genetic conditions that commonly result in sudden death in young individuals[67]. In the context of hypoxia in FD, LVH might certainly predispose affected individuals to further increased risk, given that LVH increases myocardial oxygen demand and also arrythmogenesis[68]. In terms of the four FD patients who died during this study, three of them had either electrocardiographic LVH at the time of data collection (patient 12), echocardiographic LVH at some point in time (patient 12), or both (patient 4). The only patient who died during this study who did not have any evidence for LVH was patient 11. However, an echocardiogram was also never clinically obtained from patient 11. Although five of ten of the FD patients who did not die during this study also had evidence for LVH (four of nine echocardiographically), these results nonetheless suggest that LVH may be yet another factor contributing to the risk for sudden death in FD. Examination of a larger historical FD patient database of

echocardiographic results from NYU (unpublished) demonstrates that roughly one in five FD patients who have had echocardiograms have developed at least mild degrees of echocardiographic LVH. Several patients in this larger database who did not have LVH on an initial echocardiogram later developed it, suggesting that LVH in FD might be most obviously associated with progressive, unrelenting hypertension – a condition that often goes untreated in FD due to coexisting blood pressure lability[1]. The presence of sleep apnea in FD might also exacerbate daytime hypertension and LVH[69], with untreated hypertension also likely contributing to decreased HRV[70].

It has previously been noted that abnormal repolarization, as inferred from prolonged QTc or JTc electrocardiographic intervals, may also be associated with an increased risk for syncope and sudden death in FD[5,7]. Although QTc and JTc intervals were also prolonged in FD patients (versus healthy controls) in this study, there was no clear relationship between the degree of QTc/JTc prolongation and the risk for sudden death. Several more advanced parameters of repolarization instability were also significantly increased in FD patients relative to healthy controls, including the beat-to-beat indices of QT variability and essentially all parameters of T-wave complexity derived from singular value decomposition (Table). However, none of these more advanced measures of repolarization instability was very predictive of sudden death, and in fact many of the surviving FD patients had more severe increases in these parameters than did those with sudden death. It should be recalled that structural heart disease (i.e., prior MI, LVH) and even hypertension alone[71] are associated with increased QTc intervals. Hypertension alone can also increase the QT variability index[72], whereas elevations in heart rate alone can increase the T-wave residuum[73]. Thus, the changes in

both conventional and advanced ECG parameters of repolarization in FD may be more reflective of underlying hypertension, LVH or other structural heart disease than of the propensity for sudden death per se. Finally, it should also be noted that the filtered QRS duration in this study was not different between FD patients and healthy controls, in contrast to a prior study[74], nor were parameters of HF QRS, and that these parameters were also not useful in predicting the propensity for sudden death in the FD group.

In conclusion, we found that low vagally-mediated HRV is especially predictive of the propensity for sudden death in FD patients, and that FD patients have multiple conventional and advanced electocardiographic abnormalities (compared to age- and gender-matched healthy controls) that tend to suggest structural heart disease, especially LVH. We interpret the reduced vagally-mediated HRV not so much as a direct *cause* of sudden deaths but rather as an *effect* of concurrent pathological processes, especially hypoxia, that themselves increase the risk of sudden death in FD while at the same time diminishing vagally-mediated HRV. Possible reasons for hypoxia in FD are well known and include (especially) pulmonary disease and sleep apnea. These same disease processes, along with hypertension, can also contribute to ventricular hypertrophy and to ischemic heart disease, which in turn may further exacerbate the propensity for sudden death in FD. We suggest that adenosine may play an important role in mediating episodes of vasovagal syncope, bradyarrhythmias, central respiratory depression and sudden death in FD, *possibly independently of vagal tone*, and that therefore adenosine antagonist medications such as theophylline might be useful in helping to prevent such episodes. A clinical trial that would prospectively evaluate the efficacy of methyxanthines such as theophylline in FD patients might therefore be warranted,

especially now that fundoplication and gastrostomy are so common in FD, potentially improving tolerance to methylxanthine-type medications. Finally, we suggest that vagally-mediated parameters of HRV should be followed regularly in FD (with avoidance of HRV measurements during tachycardia or dysautonomic crises), along with both electocardiographic and echocardiographic studies focused on the detection, prevention and optimal management of hypertensive heart disease.

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TABLE

ECG PARAMETERS	FAMILIAL DYSAUTONOMIA	CONTROLS	*P* VALUE	AREA UNDER ROC CURVE (If P ≤ 0.05)
Conventional ECG				
Heart Rate (beats/min)	85 ± 23	68 ± 10	0.007	0.77
PR interval (ms)	125 ± 44	148 ± 23	NS	
QRS interval (ms)	94 ± 12	93 ± 8	NS	
QTc interval (ms, Bazett-corrected)	444 ± 64	403 ± 18	0.019	0.74
JTc interval (ms, Bazett-corrected)	350 ± 57	310 ± 19	0.005	0.79
P axis (°, frontal plane)	52 ± 23	51 ± 13	NS	
QRS axis (°, frontal plane)	78 ± 15	80 ± 26	NS	
T axis (°, frontal plane)	40 ± 70	39 ± 21	NS	
12 Lead Area (uV*s)	466 ± 129	401 ± 79	NS	
12 Lead Voltage (mV)	24 ± 7	18 ± 3	0.007	0.78
Sokolow-Lyon voltage (mV)	3.3 ± 0.9	2.5 ± 0.7	0.016	0.80
Cornell Voltage (mV)	2.4 ± 1.1	1.4 ± 0.6	<0.001	0.84
Cornell Product (mV*ms)	216 ± 83	133 ± 57	0.003	0.80
P wave duration (ms)	89 ± 31	97 ± 10	NS	
Heart Rate Variability (RR interval Variability)				
SDNN (ms)	34.4 ± 18.2	55.69 ± 29.62	0.021	0.71
rMSSD (ms)	21.0 ± 11.2	51.0 ± 35.0	<0.001	0.83
pNN50 (%)	4.7 ± 6.5	26.3 ± 25.0	0.001	0.83
Triangular Index (ms)	8.2 ± 3.5	12.7 ± 5.1	0.007	0.76
TINN (ms)	122.8 ± 49.4	205.4 ± 87.2	0.003	0.80
SD1 of Poincaré plot (ms)	15.2 ± 8.3	36.2 ± 24.8	<0.001	0.82
SD2 of Poincaré plot (ms)	45.7 ± 25.0	69.5 ± 34.8	0.038	0.70
rRR of Poincaré plot (ms)	0.77 ± 0.19	0.60 ± 0.15	0.009	0.82
SD1/SD2 ratio	0.34 ± 0.17	0.50 ± 0.12	0.006	0.82
Ln VLF Power (Ln ms^2/Hz)	5.3 ± 1.5	6.1 ± 0.9	NS	
Ln LF Power (Ln ms^2/Hz)	4.9 ± 1.6	6.0 ± 1.3	0.039	0.71
Ln HF Power (Ln ms^2/Hz)	4.3 ± 1.6	6.3 ± 1.4	<0.001	0.86
Ln Total Power (Ln ms^2/Hz)	6.3 ± 1.4	7.4 ± 1.1	0.011	0.75
LF/HF ratio	2.3 ± 1.5	1.0 ± 1.1	0.013	0.79
Alpha1 (units)	1.11 ± 0.26	0.91 ± 0.22	0.035	0.71
Alpha2 (units)	1.13 ± 0.22	0.84 ± 0.17	<0.001	0.87
QT Interval Variablity				
SDNN QTV (ms, 1st Eigenvector)	3.6 ± 2.8	2.6 ± 1.5	NS	
rMSSD QTV (ms, 1st Eigenvector)	3.2 ± 4.1	1.8 ± 0.8	NS	
QTV index (units, 1st Eigenvector)	-1.56 ± 0.50	-1.94 ± 0.28	0.012	0.75
SDNN_QT (ms, lead II)	4.1 ± 3.5	2.7 ± 1.5	NS	
rMSSD_QT (ms, lead II)	3.5 ± 4.2	2.0 ± 1.1	NS	
QTV index (units, lead II)	-1.44 ± 0.49	-1.87 ± 0.26	0.002	0.83

High Frequency QRS ECG (150-250 Hz)				
RAZ score (units)	25 ± 13	36 ± 25	NS	
12-lead RMS voltage sum (uV)	60 ± 20	47 ± 21	NS	
12-lead kurtosis sum (units)	46 ± 5	45 ± 9	NS	
Reduced Amplitude Zone A (number)	5 ± 3	7 ± 3	NS	
Reduced Amplitude Zone AP (number)	3 ± 2	5 ± 3	NS	
Reduced Amplitude Zone N (number)	1 ± 1	2 ± 3	NS	
"3D ECG" parameters (using derived Frank X, Y, Z lead SAECG)				
P-wave Mean Spatial Velocity (mV/s)	5.6 ± 3.2	3.5 ± 0.5	<0.001	0.92
QRS-wave Mean Spatial Velocity (mV/s)	76.5 ± 31.2	53.7 ± 9.9	<0.001	0.86
Spatial P-wave Duration (ms)	119 ± 7	116 ± 17	NS	
Spatial Mean QRS (mV*s)	0.04 ± 0.02	0.04 ± 0.01	NS	
Mean Spatial QRS-T Angle (°)	76 ± 48	44 ± 19	0.017	0.71
Spatial Ventricular Activation Time (ms)	41 ± 5	43 ± 6	NS	
Spatial Ventricular Gradient (mV*s)	0.072 ± 0.034	0.091 ± 0.016	NS	
Maximum Spatial QRS-T Angle (°)	54 ± 41	29 ± 15	0.02	0.71
"Late Potentials" parameters (using derived Frank X, Y, Z lead SAECG, 40-250 Hz)				
Filtered QRS duration (ms)	88.0 ± 9.0	87.9 ± 9.6	NS	
RMS 40 (uV)	212.5 ± 129.0	149.7 ± 52.5	NS	
LAS (ms)	10.9 ± 9.2	13.4 ± 7.2	NS	
Waveform Complexity (by singular value decomposition and signal averaging)				
Modified complexity ratio of T wave(%)	0.56 ± 0.88	0.04 ± 0.04	0.002	0.76
PCA ratio of T wave (%)	26.6 ± 15.2	15.5 ± 4.9	0.003	0.79
Relative T-wave Residuum (%)	0.099 ± 0.157	0.008 ± 0.005	0.002	0.74
Normalized T-wave Volume (%)	2.0 ± 3.5	0.3 ± 0.2	<0.001	0.79
PCA ratio of QRS wave (%)	47.4 ± 14.4	44.8 ± 21.8	NS	
Modified complexity ratio of QRS (%)	2.1 ± 2.5	1.0 ± 0.5	0.044	0.68
Relative QRS-wave Residuum (%)	0.52 ± 0.48	0.23 ± 0.16	0.016	0.78
Normalized QRS-wave Volume (%)	5.9 ± 3.5	4.6 ± 4.0	NS	
PCA ratio of P wave (%)	30.7 ± 16.5	32.8 ± 15.4	NS	
Modified complexity ratio of P wave (%)	1.9 ± 1.3	1.1 ± 0.5	0.028	0.69
Relative P-wave Residuum (%)	0.41 ± 0.20	0.31 ± 0.15	NS	
Normalized P-wave Volume (%)	4.1 ± 3.4	3.1 ± 2.0	NS	

Values shown are means ± standard deviations. N = 14 patients with Familial Dysautonomia and 14 age- and gender matched healthy controls. ROC, receiver operating characteristic. NS, not significant. See text for parameter abbreviations.

FIG. 1

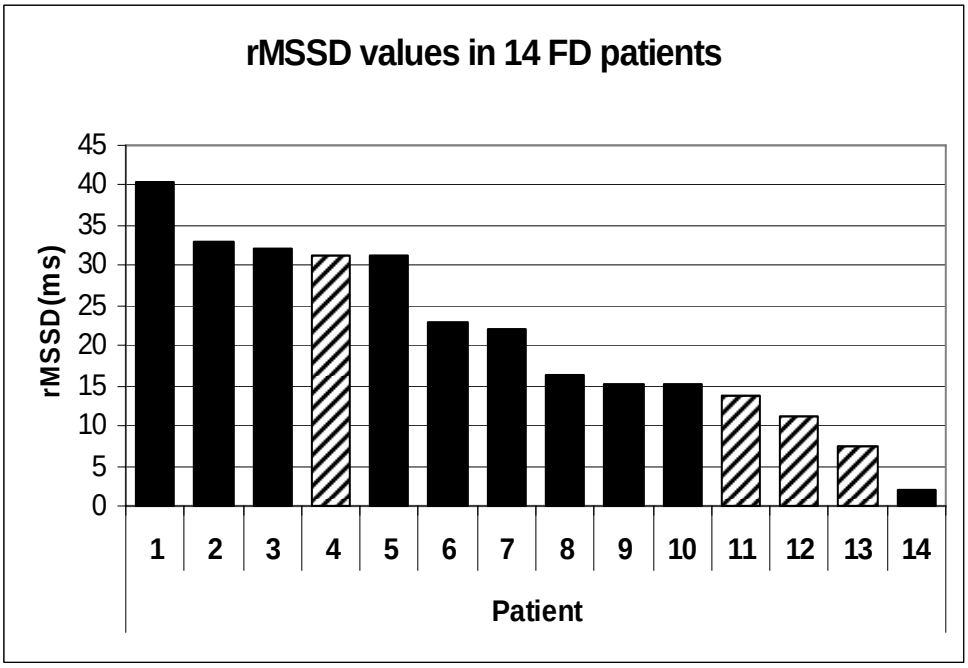
rMSSD values in 14 FD patients
rMSSD(ms)
45
40
35
30
25
20
15
10
5
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Patient

FIG. 2

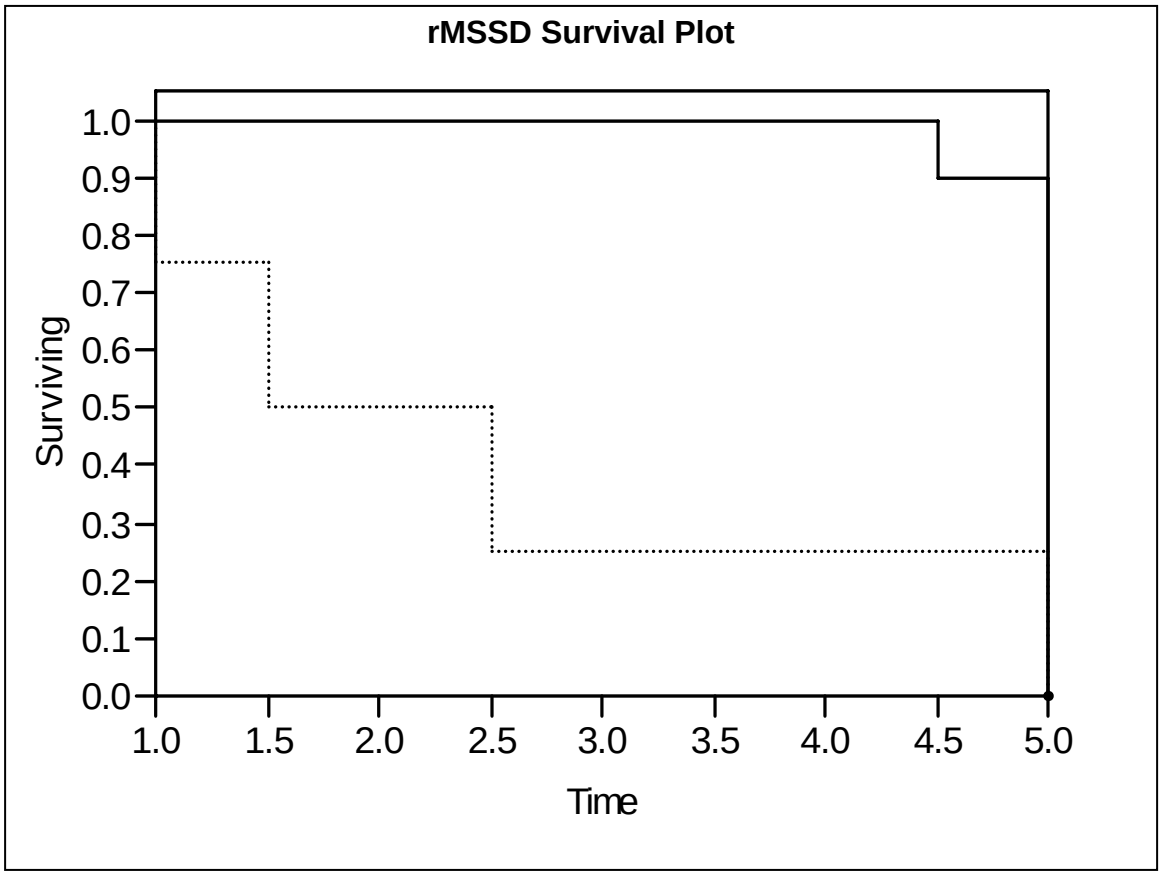
rMSSD Survival Plot
Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Time

Figure Legends:

Figure 1. Heart rate variability rMSSD values for the 14 FD patients. Living patients are represented by black bars, and the four patients who experienced sudden death by patterned bars. Although patient 4 had a normal rMSSD value at the time of index data collection (slightly less than 4.5 years prior to death), his vagally-mediated HRV parameters fell precipitously at subsequent clinical data collection points as his pulmonary disease progressed (data not shown). Sinus tachycardia was present in patients 13 and 14 and likely contributed to their low rMSSD values.

Figure 2. The solid line represents FD patients with rMSSD values > 14 ms and the dotted line FD patients with rMSSD values < 14 ms. Time represents time in years from the index data collection, and Surviving the proportion of individuals in the given rMSSD group still alive at the given Time.