

Original article

Electrocardiographic QT interval and cardiovascular reactivity in fibromyalgia differ from chronic fatigue syndrome

Jochanan E. Naschitz^{a,*}, Gleb Slobodin^a, Dauod Sharif^b, Madeline Fields^a, Hillel Isseroff^a, Edmond Sabo^a, Itzhak Rosner^c

^a Departments of Internal Medicine A, Bnai Zion Medical Center and 'Rappaport Family' Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

^b Heart Institute, Bnai Zion Medical Center and 'Rappaport Family' Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

^c Rheumatology, Bnai Zion Medical Center and 'Rappaport Family' Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Received 17 February 2007; received in revised form 27 August 2007; accepted 30 August 2007

Available online 19 November 2007

Abstract

Background: Fibromyalgia (FM) and chronic fatigue syndrome (CFS) frequently overlap clinically and have been considered variants of one common disorder. We have recently shown that CFS is associated with a short corrected electrocardiographic QT interval (QTc). In the present study, we evaluated whether FM and CFS can be distinguished by QTc.

Methods: The study groups were comprised of women with FM ($n=30$) and with CFS ($n=28$). The patients were evaluated with a 10 min supine–30 min head-up tilt test. The electrocardiographic QT interval was corrected for heart rate (HR) according to Fridericia's equation (QTc). In addition, cardiovascular reactivity was assessed based on blood pressure and HR changes and was expressed as the 'hemodynamic instability score' (HIS).

Results: The average supine QTc in FM was 417 ms (SD 25) versus 372 ms (SD 22) in CFS ($p<0.0001$); the supine QTc cut-off <385.7 ms was 79% sensitive and 87% specific for CFS vs. FM. The average QTc at the 10th minute of tilt was 409 ms (SD 18) in FM versus 367 ms (SD 21) in CFS ($p<0.0001$); the tilt QTc cut-off <383.3 ms was 71% sensitive and 91% specific for CFS vs. FM. The average HIS in FM patients was -3.52 (SD 1.96) versus $+3.21$ (SD 2.43) in CFS ($p<0.0001$).

Conclusion: A relatively short QTc and positive HIS characterize CFS patients and distinguish them from FM patients. These data may support the contention that FM and CFS are separate disorders.

© 2007 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

Keywords: Fibromyalgia; Chronic fatigue syndrome; Electrocardiography; QT interval; Cardiovascular reactivity; Fractal analysis

1. Introduction

Fibromyalgia (FM) is a clinical syndrome characterized by widespread pain and abnormal sensitivity on palpation of specific tender points [1]. The pathogenesis of FM has been elusive, made difficult by the absence of distinctive biochemical or histological abnormalities. The very concept

of FM has been challenged with suggestions that it represents an inappropriate extraction from the epidemiological continuum of subjective discomfort [2]. The clinical overlap of FM and chronic fatigue syndrome (CFS) reported to a variable extent has led to their frequent consideration as a single disorder [3–5]. On the other hand, support for FM as a distinct entity may be offered were a characteristic feature to be found which demarcates this group from the rest of the population [5]. Such evidence may be obtained from the study of the autonomic nervous system, which has been widely reported to be aberrant in FM [6–11].

* Corresponding author. Department of Internal Medicine A, Bnai Zion Medical Center, Haifa 31048, P.O. Box 4940, Israel.

E-mail address: Naschitz@tx.technion.ac.il (J.E. Naschitz).

In the clinical setting, autonomic nervous system activity is assessed by surrogate methods, chiefly cardiovascular reactivity (CVR). The fast response of the blood pressure (BP) and heart rate (HR) to acute stimuli is under autonomic nervous control. Therefore, BP and HR measurements during orthostatic challenge on head-up tilt testing (HUTT) can be used as one measure of cardiovascular autonomic activity, providing there is no evidence of organic heart disease, venous insufficiency or hypovolemia [12]. Classical pathological reactions to the HUTT are: vasodepressor reaction, cardioinhibitory reaction, orthostatic hypotension and postural tachycardia syndrome. In studies utilizing these outcome measures, evidence for abnormal cardiovascular reactivity was found in up to 60% FM patients [13]. However, these aberrations of CVR are considered to be nonspecific since the same reactions occur in a large variety of conditions associated with autonomic dysfunction [14]. Study of HR variability in FM patients has shown abnormalities consistent with sympathetic hyperactivity at rest and hyporeactivity to orthostatic stress [15–17] which is nonspecific, also occurring in a variety of other conditions associated with autonomic dysfunction [15,16]. By applying a novel method for the study of cardiovascular reactivity, an abnormal autonomic system functioning has been recognized in patients with CFS that differs from classic autonomic failure [6,7]. This method involves computing BP and HR changes during the course of a head-up tilt test with data processing by image analysis methods. These data receive numerical expression as the ‘hemodynamic instability score’ (HIS). HIS values > -0.98 are associated with CFS — sensitivity 84.5% and specificity 85% [7]. In contrast, by application of this methodology to FM, affected persons could not be distinguished from a normal population [6,8].

Changes in autonomic nervous activity also condition the repolarization kinetics of myocardial cells and, thereby, may modify the electrocardiographic QT interval [18–21]. In a recent study, a relatively short QT interval was found to be characteristic of CFS patients [22]. In the present study we examined whether QT intervals as well as cardiovascular reactivity differ in FM versus CFS.

2. Patients and methods

All participants gave informed consent and our institution’s committee for human research approved the study. All patients were fully ambulatory at the time of the study. Technicians carrying out the HUTT were informed as to the patients’ diagnosis but did not know of the intention to compare between the groups. Tilt test recordings of previously studied patients [23,24] were reevaluated. Consecutive female patients presenting either FM or CFS having completed 30 min of head-up tilt were selected for this analysis. Not included were subjects with comorbidities (such as obesity, diabetes mellitus) as well as those with overlapping FM and CFS. The FM patients ($n=30$) met the criteria of the American College of Rheumatology for FM

[1]. The average number of tender points was 14.7 (SD 1.7). All patients had normal sedimentation rate, creatine kinase, and thyroid stimulating hormone levels and there was no evidence of any concomitant inflammatory rheumatic disorder. Their average age was 46.8 years (SD 7.1) and their average body mass index was 25.4.3 (SD 1.4). CFS patients ($n=28$) met the Centers of Disease Control and Prevention definition criteria of CFS [25]. Their average age was 35.8 years (SD 15.1) and their average body mass index was 25.1 (SD 1.4).

2.1. Head-up tilt test (HUTT)

The protocol of the HUTT was based on the 10-min supine–30 min head-up tilt test as previously described [6]. Testing was conducted from 8:00 a.m. to 11:00 a.m., in a quiet environment, and at a constant room temperature of 22–25 °C. The patients maintained a regular meal schedule, but were restricted from smoking and caffeine ingestion within 6 h of the examination. Intake of food products and medications with sympathomimetic activity prior to the study was prohibited. The patients lay in a supine position on the tilt table, secured to the table at the chest, hips and knees with adhesive girdles. Chest electrodes were placed on the right and left shoulders just below the clavicles and a third electrode was applied at the point where the left axillary line intersected the fifth intercostal space. The ECG was recorded on a Datex–Engstrom Cardiocap™ II instrument (Datex Instrumentation Corporation, Helsinki, Finland), connected to the Biopac MP 100 data acquisition system (Biopac, Santa Barbara, California). A sampling rate of 500 per second provided 1/500 Hz resolution. ECG tracings obtained corresponded to aVL, but when inappropriate measurements were obtained a chest modified lead V5 was utilized. Continuous ECG tracings were acquisitioned. The cuff of the BP recording device was attached to the left arm, which was supported at heart level at all times during the study. The stored data were later assessed by independent investigators who computed the hemodynamic instability score (HIS) and measured the QT and RR intervals.

2.2. Measurement of the QT interval

The ECG recordings were displayed on the computer screen at 50 mm/s speed with appropriate magnification for adequate identification of the T wave. The QT interval was measured from the beginning of the QRS complex to the point at which the T wave returned to the isoelectric line. When a U wave was present, the end point of the T wave was defined as the intersection of the steepest slope of the descending T wave and the isoelectric line [26]. The QT and RR intervals were measured by using the caliper of the Biopac computer program. Samples of 10 consecutive RR and QT intervals were measured a) at the end of 10 min of recumbence and b) at the end of 10 min of head-up tilt. The median value of each set of measurements represents the RR

interval and the uncorrected QT interval, respectively. Coefficients of variation of the QT measurements have been previously established in two observers (MF and JEN): the intraobserver variation was 2.18% and 1.9%, respectively; the interobserver variation was 2.25% and 2.19%, respectively. Fridericia's equation performed the best to eliminate the effect of the HR on QT [22,27]. Fridericia's equation [28]:

$$QTc = QT/RR^{1/3}$$

The best QTc cut-offs, separating CFS patients from a mixed control population (not including FM patients) were supine <385.7 ms and at the 10th minute of tilt <383.3 ms [22]. In the latter study, QTc values in healthy subjects were: supine average 396 ms (SD 26) and tilt 400 ms (SD 39). In the present study, the sensitivity of these cut-off values for CFS and their specificity vs. FM was reassessed.

The HIS was determined according to the protocol previously described [6]. Several preliminary measurements were done, the first of them being calculation of the 'BP change' and 'HR change'. The BP and HR changes were also represented graphically in time-curves. The images were loaded in the computerized image analyzer Benoit Version 1.3 (Trusoft Int'l, Inc, 1999, St. Petersburg, Florida). The fractal dimension was automatically assessed by using the box counting method. Based on BP and HR changes and fractal dimension, an equation permitted to compute the 'hemodynamic instability score' (HIS).

$$\begin{aligned} HIS = & 64.3303 + (SYST-FD.abs \times -68.0135) \\ & + (SYST-SD.cur \times 111.3726) + HR-SD.cur \\ & \times 60.4164 \end{aligned}$$

The following independent predictors of the discriminant score were applied in this equation: the absolute value of systolic BP changes (SYST-FD.abs), the standard deviation of the current values of the systolic BP changes (SYST-SD.cur), and the standard deviation of the current values of the heart rate changes (HR-SD.cur). For reference, in 60 healthy subjects of whom 36 were women and the average age was 28.6 years (SD 8.3), HIS average was -3.14 (SD 2.9).

2.3. Statistical analysis

The difference between averages of two groups was assessed by unpaired Student's *t* test. Two-tailed *p* values of 0.05 or less were considered to be statistically significant.

3. Results

3.1. Supine QTc values

Supine QTc values had a normal distribution. The average supine QTc in FM patients was 417 ms (SD 25). The average supine QTc in CFS patients was 372 ms (SD 22). The difference between averages was 45 ms, the 95% CI 32–58,

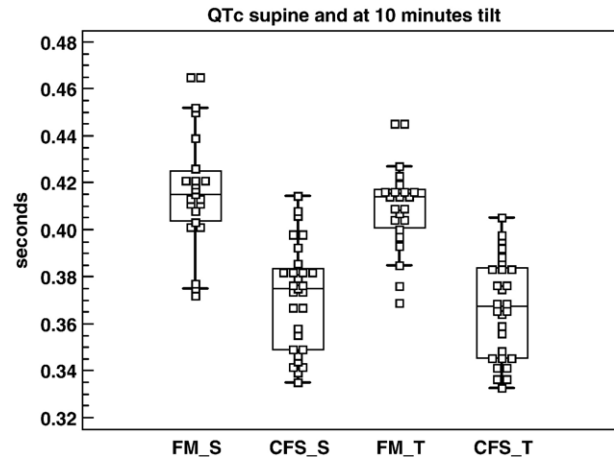


Fig. 1. QTc values in FM and CFS. FM_S = fibromyalgia patient measurements at the end of the supine phase, CFS_S = CFS patient measurements at the end of the supine phase; FM_T = FM patient measurements at 10 min of tilt; CFS_T = CFS patient measurements at 10 min of tilt. The boxes contain the 50% of values falling between the 25th and 75th percentiles; the horizontal line within the box represents the median value; the 'whiskers' are the lines that extend from the box to the highest and lowest values excluding the outliers.

$p < 0.0001$ (Fig. 1). The supine QTc cut-off <385.7 ms had 79% sensitivity for CFS and 87% specificity vs. FM.

3.2. Tilt QTc values

Tilt QTc values had a normal distribution. The average QTc in FM patients during the 10th minute of tilt was 409 ms (SD 18 ms). The average QTc in CFS patients at 10th minute tilt was 367 ms (SD 21). The difference between averages was 43 ms, the 95% CI 32–54, $p < 0.0001$. The tilt QTc cut-off <383.3 ms had 71% sensitivity for CFS and 91% specificity vs. FM.

3.3. HIS values

The average HIS value in FM patients was -3.52 (SD 1.96), with only one patient exceeding the -0.98 cut-off. The average HIS value in CFS patients was +3.21 (SD 2.43), being greater than -0.98 in all patients. The intergroup difference was statistically significant ($p < 0.0001$).

4. Discussion

In this study, the QTc was within the normal range in the large majority of FM patients (average 417 ms supine and average 409 ms on tilt) while a relatively short QTc interval characterized CFS patients (average supine QTc 372 ms and average tilt QTc 367 ms).

The QT interval on the surface electrocardiogram (ECG) reflects depolarization and repolarization of myocardial cells. A variety of factors may influence the QT interval, including heart rate (HR), genetic abnormalities of the potassium channel, electrolyte disturbances, myocardial

ischemia, drugs, and sympathetic and parasympathetic tone [19,21]. The HR influences the QT interval to a considerable extent, therefore, for common use, the QT is adjusted to HR (QTc). The methodology of QT correction utilized in this study is well established. The reproducibility of QT measurements was demonstrated by low intraobserver and interobserver variabilities and compared favorably with data published elsewhere [22,27–29]. In comparisons of 10 different QT correction formulas, Fridericia's correction was shown to provide the best results [29]. We tested various correction formulas in our patient population [22] and found, in fact, that Fridericia's correction performed the best and was, therefore, selected for the present investigation.

Usually QTc in the range of 0.400–0.440 s is considered to be normal [30]. While the upper limit of normal for the QTc is well defined and its prolongation has been used as an ECG marker to identify patients at risk for sudden arrhythmogenic death, there is no consensus on the lower limit of normal for the QTc or its clinical significance. Atropine causes QTc shortening [19]. Short QT intervals are encountered in hypercalcemia [31] and the recently described idiopathic rate-independent short QT syndrome [32]. A relatively short QTc is often noticed in patients with the chronic fatigue syndrome [22].

The mechanisms underlying the relatively short QTc in CFS have not been investigated. Prior studies in CFS, based on spectral analysis of HR and BP, showed that the vagal tone is reduced in these patients [33,34]. Decreased vagal tone may provide the mechanism for QTc shortening in CFS; however, it should be noted that not all studies have confirmed that vagal tone is diminished in CFS [35,36].

The HIS, which reflects autonomic nervous influences on the cardiovascular system, HIS differs significantly in FM versus CFS. In the present study, the average HIS in FM was -3.52 (SD 1.96) and the average HIS in CFS was $+3.21$ (SD 2.43) ($p < 0.0001$). This data is consistent with previous results in female FM and CFS patients and compared to healthy controls. In one study [6], the HIS threshold -0.98 differentiated between CFS patients (HIS = average $+2.02$, SD 4.07) on one hand and healthy subjects (HIS = average -2.48 , SD 4.07, $p < 0.0001$) as well as FM (HIS average -3.27 ± 2.63 , $p < 0.0001$) on the other hand. Subsequent studies confirmed these observations [7,8]. The overall specificity of the HIS for the diagnosis of CFS was 85% [23].

FM and CFS overlap has been repeatedly reported and raised the possibility that both conditions are variants of one common functional disorder [3–5]. Recent studies addressed the molecular basis of CFS. Data from the Wichita (KS, USA) CFS Surveillance Study identified 24 common genes in CFS patients, providing evidence for a biological basis of CFS [37]. A different possible genetic association has been reported in FM with a polymorphism in the serotonin transporter gene regulatory region [38]. Other scientists are skeptical with these results. Additional studies have suggested that CFS patients may be distinguished from those with FM by their cardiovascular reactivity pattern

[24,39]. In the present study, the QTc and HIS were within the normal range in the large majority of FM patients. In contrast, a short QTc interval and increased HIS characterized CFS patients. Both HIS and QTc are influenced by autonomic nervous activity. Thus, an alteration in autonomic function which is operative in CFS but not in FM may explain the differences in QTc and HIS. A recent review article by Prins et al. [40] recapitulates the difficulties with the definition and understanding the pathophysiology of CFS. The authors suggest a framework for future studies by following two strategies: the aims at distinguishing CFS from other disorders; the other explores similarities and dissimilarities in functional somatic syndromes based on neurosciences. Applying the methodology of QTc and HIS in the study of autonomic functions in CFS and FM may be in line with those suggestions.

There are limitations to this study. Patients with FM and CFS were not of similar age; only milder cases of CFS were studied; patients with FM-CFS comorbidity were not included; and detailed assessment of autonomic nervous functions has not been performed. There are also limitations related to the methodology utilized. Only one monitor lead was used to measure the QT intervals and not the 12 lead electrocardiogram. This restriction was a function of the monitoring instrument used.

Combined evaluation of the cardiovascular reactivity and cardiac depolarization–repolarization may be of interest in research settings. Their applicability in clinical situations and their possible advantage as a diagnostic test remains to be investigated in prospective studies. In the future, electrophysiological studies and investigations of family members of CFS patients may be important to the understanding of the pathophysiology of shortened QTc in CFS and establish to what extent this phenomenon is inherited.

5. Learning points

- Fibromyalgia and chronic fatigue syndrome frequently overlap clinically and have been considered to be variants of one common disorder. Changes in autonomic nervous activity have been linked to the pathophysiology of both disorders.
- The present study showed that autonomic nervous functioning, indirectly evaluated via electrocardiographic QTc interval and cardiovascular reactivity, differs in fibromyalgia and chronic fatigue syndrome.
- This data may support the contention that fibromyalgia and chronic fatigue syndrome are separate disorders.

References

- [1] Wolfe F, Smythe A, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33:160–72.
- [2] Rau CL, Russell IJ. Is fibromyalgia a distinct clinical syndrome? *Curr Rev Pain* 2000;4:287–94.

- [3] Ciccone DS, Natelson BH. Comorbid illness in women with chronic fatigue syndrome: a test of the single syndrome hypothesis. *Psychosom Med* 2003;65:268–75.
- [4] Wessely S, Chalder T, Hirsch S, Wallace P, Wright D. Psychological symptoms, somatic symptoms, and psychiatric disorder in chronic fatigue and chronic fatigue syndrome: a prospective study in the primary care setting. *Am J Psychiatry* 1996;153:1050–9.
- [5] Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia and temporomandibular disorder. *Arch Intern Med* 2000;160:221–7.
- [6] Naschitz JE, Sabo E, Naschitz S, Shaviv N, Rosner I, Rozenbaum M, et al. Hemodynamic instability in chronic fatigue syndrome: indices and diagnostic significance. *Semin Arthritis Rheum* 2001;31:199–208.
- [7] Naschitz JE, Sabo E, Naschitz S, Rosner I, Rozenbaum M, Fields M, et al. Hemodynamic instability score in chronic fatigue syndrome (CFS) and non-CFS chronic fatigue. *Semin Arthritis Rheum* 2002;32:141–8.
- [8] Naschitz JE, Rozenbaum M, Rosner I, Sabo E, Priselac RM, Shaviv N, et al. Cardiovascular response to upright tilt in fibromyalgia differs from that in chronic fatigue syndrome. *J Rheumatol* 2001;28:1356–60.
- [9] Rautaharju PM, Warren JW, Calhoun HP. Estimation of QT prolongation. A persistent, avoidable error in computer electrocardiography. *J Electrocardiol* 1990;23(Suppl):111–7.
- [10] Ewing DJ, Nollson JM. QT interval length and diabetic autonomic neuropathy. *Diabet Med* 1990;7:23–6.
- [11] Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, Van Raay TJ. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nature Genetics* 1996;12:17–23.
- [12] Bou-Holaigah I, Calkins H, Flynn JA, Tunin C, Chang HC, Kan JS, et al. Provocation of hypotension and pain during upright tilt table testing in adults with fibromyalgia. *Clin Exp Rheumatol* 1997;15:239–46.
- [13] Wieling W, Karemaker JM. Measurement of heart rate and blood pressure to evaluate disturbances in neurocardiovascular control. In: Mathias Ch J, editor. *Autonomic failure. A textbook of clinical disorders of the autonomic nervous system*. Fourth edition. Oxford University Press; 1999. p. 198–210.
- [14] Parati G, DiRienzo M, Omboni S, Mancia G. Computer analysis of blood pressure and heart rate variability in subjects with normal and abnormal autonomic cardiovascular control. In: Mathias CJ, Bannister R, editors. *Autonomic failure. A textbook of clinical disorders of the autonomic nervous system*. Fourth edition. Oxford University Press; 1999. p. 211–23.
- [15] Cohen H, Neumann L, Alhoshhle A, Kotler M, Abu-Shakra M, Buskila D. Abnormal sympathovagal balance in men with fibromyalgia. *J Rheumatol* 2001;28:581–9.
- [16] Raj SR, Brouillard D, Simpson CS, Hopman WM, Abdollah H. Dysautonomia among patients with fibromyalgia: a noninvasive assessment. *J Rheumatol* 2000;27:2660–5.
- [17] Martinez-Lavin M, Hermosillo AG, Rosas M, Soto ME. Circadian studies of autonomic nervous balance in patients with fibromyalgia: a heart rate variability analysis. *Arthritis Rheum* 1998;41:1966–71.
- [18] Milne JR, Camm AT, Ward DE, Spurrill RA. Effect of intravenous propranolol on QT interval: a new method of assessment. *Br Heart J* 1980;43:1–6.
- [19] Browne KF, Zipes DP, Heger JJ, Prystowsky EN. Influence of the autonomous nervous system on the QT interval in man. *Am J Cardiol* 1982;50:1099–103.
- [20] Silvieri R, Vegho M, Chinaglia A, Scaglione P, Perin PC. Prevalence of QT prolongation in a type 1 diabetic population and its association with autonomic neuropathy. The Neuropathy Study Group of the Italian Society for the Study of Diabetes. *Diabet Med* 1993;10:920–4.
- [21] Choy AMJ, Lang CJ, Roden DM, Robertson D, Wood AJJ, Robertson RM, et al. Abnormalities of the QT in primary disorders of autonomic failure. *Am Heart J* 1998;136:664–71.
- [22] Naschitz JE, Fields M, Isseroff H, Sharif D, Sabo E, Rosner I. Shortened QT interval: a distinctive feature of the dysautonomia of chronic fatigue syndrome. *J Electrocardiology* 2006;39:389–94.
- [23] Naschitz JE, Sabo E, Dreyfuss D, Yeshurun D, Rosner I. The head-up tilt test in the diagnosis and management of chronic fatigue syndrome. *Isr Med Assoc J* 2003;5:807–11.
- [24] Naschitz JE, Rozenbaum M, Fields M, Enis S, Manor H, Dreyfuss D, et al. Cardiovascular reactivity in fibromyalgia: evidence for pathogenic heterogeneity. *J Rheumatol* 2005;32:335–9.
- [25] Fukuda K, Straus SE, Mickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Study Group. *Ann Intern Med* 1994;121:953–9.
- [26] Lepeschkin E, Surawicz B. The measurement of the Q–T interval of the electrocardiogram. *Circulation* 1952;5:378–88.
- [27] Puddu PE, Jouve R, Marriotti S, Giampaoli S, Lanti M, Reale A, et al. Evaluation of 10 QT prediction formulas in 881 middle-aged men from the Seven Countries Study: emphasis on the cubic root Fridericia's equation. *J Electrocardiol* 1988;21:219–29.
- [28] Fridericia LS. Die Systolendauer in Elektrokardiogramm bei normalen Menschen und bei Herzkranken. *Acta Med Scand* 1920;53:469–86.
- [29] Veglio M, Maule S, Matteoda C, Quadri R, Valentini M, Pechio O, et al. Use of corrected QT interval in autonomic function testing: assessment and reproducibility. *Clin Auton Res* 1996;6:309–12.
- [30] Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QT interval variables from 24 hour electrocardiography and the two year risk of sudden death. *Br Heart J* 1993;70:43–8.
- [31] Nierenberg DW, Ransil BJ. Q-aTc interval as a clinical indicator of hypercalcemia. *Am J Cardiol* 1979;44:243–8.
- [32] Gussak I, Brugada P, Brugada J, Wright RS, Kopecky SL, Chaitman BR, et al. Idiopathic short QT interval: a new clinical syndrome? *Cardiology* 2000;94:99–102.
- [33] Sisto SA, Tapp W, Drastal S, Bergen M, DeMasi I, Cordero D, et al. Vagal tone is reduced during paced breathing in patients with the chronic fatigue syndrome. *Clin Auton Res* 1995;5:139–43.
- [34] Cordero DL, Sisto SA, Tapp WN, LaManca JJ, Pareja JG, Natelson BH. Decreased vagal power during treadmill walking in patients with chronic fatigue syndrome. *Clin Auton Res* 1996;6:329–33.
- [35] Duprez DA, De Buyzere ML, Drieghe B, Vanhaverbeke F, Taes Y, Michielsen W, et al. Long- and short-term blood pressure and RR-interval variability and psychosomatic distress in chronic fatigue syndrome. *Clin Sci (Lond)* 1998;94:57–63.
- [36] Soetekouw PM, Lenders JW, Bleijenberg G, Thien T, van der Meer JW. Autonomic function in patients with chronic fatigue syndrome. *Clin Auton Res* 1999;9:334–40.
- [37] Fang H, Xie Q, Boneva R, Fostel J, Perkins R, Tong W. Gene expression profile exploration of a large dataset on chronic fatigue syndrome. *Pharmacogenomics* 2006;7:429–40.
- [38] Offenbaecher M, Bondy B, de Jonge S, Glatzeder K, Krüger M, Schoeps P, et al. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. *Arthritis Rheum* 1999;42:2482–8.
- [39] Naschitz JE, Rosner I, Rozenbaum M, Fields M, Isseroff H, Babich JP, et al. Patterns of cardiovascular reactivity in disease diagnosis. *QJM* 2004;97:141–51.
- [40] Prins JB, van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. *Lancet* 2006;367:346–55.