ORIGINAL ARTICLE

Analysis of the Incidence and Clinical Significance of Long and Short Corrected QT Interval in Electrocardiogram in Healthy Population of Changsha in China

L Liu[1,2], C Wang[2], P Lin[2], R Zou[2], L Wu[2], D Mao[2], Z Xie[2]

ABSTRACT

Objective: *To analyse the incidence of long and short corrected QT (QTc) in a healthy sample of the population of Changsha in China.*

Methods: *Standard 12-lead electrocardiograms (ECGs) were performed on 4025 subjects in Changsha of China, whose age ranged from 6 minutes after birth to 83 years, between January 1993 and December 2012. Heart rate and QT interval were measured and recorded. Corrected QT was calculated with Bazett´s formula ($QTc = QT/RR^{0.5}$). All recruited individuals had taken healthy examination, ruling out general health issue, in The Second Xiangya Hospital of Central South University. Statistical analyses were performed using the SPSS 16.0 software (IBM Corp, Armonk, NY, USA).*

Results: *The incidence of short QTc was 7.13% (287/4025 cases). The peak values of the incidence were in the 30–40 years group (15.71%). The low values were in the 1–3 months group and 3–6 months group (0%, 0.76%), respectively. The incidence of long QTc was 3.16% (127/4025 cases). The values diminished significantly after adulthood. The low values were in the age groups of 18–30 years (0.86%) and 30–40 years (0.71%), respectively. After the age of 50 years, the incidence of long QTc increased with age 50–60 years and 60–70 years and 70–83 years (7.89%, 9.06%, 14.06%), respectively. There was no statistically significant difference between the genders (*$p > 0.05$*).*

Conclusion: *The peak incidences of long and short QTc existed in two separate age groups in the healthy sample. The peak incidence of short QTc was in the age group of 18–40 years, and the peak incidence of long QTc was in the age group beyond the 50 years. For these two age groups, it was recommended to pay close attention to the changes in their QTc in order to prevent cardiovascular events.*

Keywords: Electrocardiography, long corrected QT interval, short corrected QT interval.

INTRODUCTION

The QT interval of standard 12-lead electrocardiograms (ECGs) represents the time from the onset of ventricular depolarization (onset of the Q wave) to the completion of ventricular repolarization (end of the T wave) (1), and also ventricular electrical contraction time. In the pathologic condition, electrical contraction changes much earlier and more sensitively than the mechanical one. Abnormal ventricular repolarization may induce the shortening or extending of QT interval, which indicates the instability of ventricular electrical conduction, causing ventricular arrhythmia, syncope, spasm, and even sudden death (2). Algra *et al* (3) discovered that the risk of sudden death existed in the patients with long and short QT interval (< 400 ms). The corrected QT (QTc) extension and shortening would bring on average two

From: [1]Department of Pediatric Cardiology, Hunan People's Hospital/ First Affiliated Hospital of Hunan Normal University, Changsha, Hunan, China and [2]Department of Pediatric Cardiovasology, Children's Medical Center, The Second Xiangya Hospital of Central South University/Institute of Pediatrics of Central South University, Changsha, Hunan, China.

Correspondence: Prof. Cheng Wang, Department of Pediatric Cardiovasology, Children's Medical Center, The Second Xiangya Hospital of Central South University/Institute of Pediatrics of Central South University, People's Road No.139, Changsha, Hunan 410011, China. Email: wangcheng2nd@126.com

 DOI:107727/wimj.2015.420

times more risk of sudden death than the normal QTc (400–440 ms). The relative risk of QT interval extension was 2.3, while the QT interval diminishing was 2.4. QT interval is affected mostly by various factors, such as heart rate, age, gender, adrenaline, autonomic nerve tension, among others (4), of which the most significant is the heart rate. In order to rectify the influence of heart rate on QT interval, the Bazett′s square root correction formula ($QTc = QT/RR^{0.5}$) was adopted since Bazett put it forward in 1920 (5). Autonomic nerve system is the important regulatory mechanism of ventricular repolarization, whose function declines with age, impaired baroreceptor caused by arterial wall stiffness and so on (6). The QT interval is also regulated by the autonomic nerve. The function of the autonomic nerve through the activity of the sympathetic and the parasympathetic nerve on QT interval is complex. Clinical researches also showed that long QT interval syndrome (LQTS) and short QT interval syndrome (SQTS) could result in malignant arrhythmia, which is always associated with the autonomic nerve function changing and the rise of ventricular repolarization heterogeneity (7). Cardiac automatic nerve matures in childhood, reaching to its fastigium in puberty; on the other hand, the carotid artery elasticity declines with age (8). Therefore, we assume that the incidence of short and long QTc intervals was obviously different in certain subgroups of age groups. The aim therefore of this study was to find out the high incidence of long and short QTc age groups in a healthy sample, before they had the clinical symptoms, and to focus on those high incidence age groups to prevent cardiovascular events.

SUBJECTS AND METHODS

We recruited many Changsha's people who were taking physical examinations in The Second Xiangya Hospital of Central South University in Changsha of China from January 1993 to December 2012, including government functionaries, workers, students (college, high school and primary school), kindergarteners and newborn infants from the obstetrics department. All the subjects had been excluded from cardiovascular diseases through their detailed medical history collected and their physical examinations. The research subjects over 60 years of age met the following criteria: moved with ease, had no history of cardiovascular drugs, had no abnormal signs in their cardiac examinations, had normal blood pressure, had no cardiomegaly in echocardiography and heart X-ray tests, their left ventricular and aorta contracted normally, had normal serum electrolytes, had normal serum lipid, and had normal blood glucose. In all, we collected 4025 cases, including 2207 cases of males, 1818 cases of females, age ranging from newborn in 6 minutes to 83 years. They were classified into 14 age groups (9) as follows: newborn, 1 month, 3 months, 6 months, 1 year, 3 years, 5 years, 8 years, 12 years, 18 years, 30 years, 40 years, 50 years, and 60–83 years. Each age group was further divided into subgroups of males and females. The distribution characteristics of age, gender and group cases are listed in the Table.

Table: Age and gender distributions of long and short QTc in ECG among Changsha healthy people (cases)

Age group	Total (case)	Male (case)	Female (case)
Newborn	457	393	850
1 month	89	66	155
3 months	75	57	132
6 months	66	62	128
1 year	152	100	252
3 years	74	84	158
5 years	104	69	173
8 years	170	183	351
12 years	239	209	448
18 years	122	110	232
30 years	142	138	280
40 years	129	115	244
50 years	153	151	304
60 years to 83 years	235	83	318
Total	4025	2207	1818

Electrocardiogram

Siemens and Japan photoelectrical electrocardiographs were adopted to record the participants' body surface ECG. The subjects took a 15-minute rest to minimize the tension interference. Electrocardiogram electrodes were placed routinely, and the electrode diameter varied according to the ages, in order to avoid local interference. The gain was 10 mm/mV, and speed was 25 mm/s; filter unit was not applied. Each record of ECG should have smooth baseline, without significant interference and clear graphics. The QT interval of the ECG was measured by two specialists independently. A third person made the final judgement when different opinions occurred. The QT interval was the time from the beginning of the QRS wave to the end of the T wave of the ECG.

Diagnostic criteria

We calculated QTc with the Bazett′s square root correction formula ($QTc = QT/RR^{0.5}$). A $QTc < 360$ ms indicated that QTc was shortened (10), and $QTc \geq 450$ ms of male or $QTc \geq 460$ ms of a female indicated that the QTc was prolonged (11).

Statistical analyses

Each measured value was stored in the computer respectively according to the subjects' gender, age (minute, hour, day, month, year), number, and feature. The SPSS 16.0 software (IBM Corp, Armonk, NY, USA) was used to calculate the descriptive parameters, *eg*, ages were compared with the F test, two-by-two were compared with the Q test, male and female were compared with the *t* test. $p < 0.05$ indicated that there was a significant statistical difference.

RESULTS

The incidences of long and short QTc of each age group did not change linearly.

Short QTc incidence

The total incidence of short QTc was 7.13% (287 in 4025 cases), reaching to its maximum in these three age groups: 18–30 years, 30–40 years and 40–50 years, which was 15.09% (35 in 232 cases), 15.71% (44 in 280 cases) and 13.11% (32 in 244 cases), respectively. However, the rates of the age groups of 1–3 months and 3–6 months were the lowest, 0% (0 in 155 cases) and 0.76% (1 in 132 cases), respectively. The incidence of the children (< 18 years) was 5.89% (156 in 2647 cases), which (≥ 18 years) was 9.51% (131 in 1378 cases) in the adults.

Long QTc incidence

The total incidence of long QTc was 3.16% (127 in 4025 cases), and there was no obvious difference in all the age groups of children. However, it diminished dramatically in adulthood, reaching the trough in 18–30 years and 30–40 years groups, in which it was 0.86% (2 in 232 cases) and 0.71% (2 in 280 cases), respectively. It gradually rose with the age from 50 years, reaching the peak in the groups of 50–60 years, 60–70 years and 70–83 years, in which it was 7.89% (24 in 304 cases), 9.06% (23 in 254 cases) and 14.06% (9 in 64 cases) respectively. The incidence in the children (< 18 years) was 2.34% (62 in 2647 cases). The incidence in the adult (≥ 18 years) was 4.72% (65 in 1378 cases) (Figure).

Gender differences

The comparison of the incidences between the males and females of all the subjects and between each group had no statistically significant difference.

DISCUSSION

In this study, the total incidence of short QTc was 7.13%, and the incidences between the males and the females

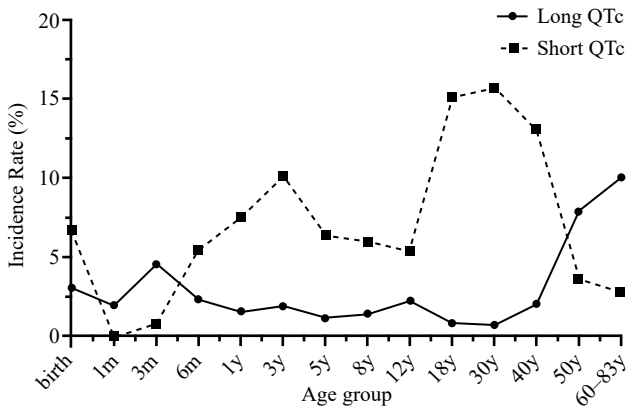

Figure: The incidence of long and short corrected QT (QTc) of different ages and gender of health people in Changsha.

of all the subjects in each group had no statistically significant difference. Anttonen *et al* (12) followed up 10 822 cases of people of middle age (5658 cases of males, from 30 to 59 years, average age 44 ± 8.4 years); the percentage of QTc < 360 ms was 2.9% (males 4.4%, females 1.3%, $p < 0.01$). There was no statistically significant difference of sudden death caused by all kinds of reasons or cardiovascular factors between the short QTc group and the normal QTc group. This study showed that the incidence of 30-59 years age group was 10.51%, the data were higher than those of Anttonen's. Consideration should be given to the possibility of small sample size and racial differences in this study and Anttonen's. Viskin *et al* (10) defined a short QTc of ≤ 360 ms in males and ≤ 370 ms in females, and reported that in the patients with idiopathic ventricular fibrillation (VF), the males' short QTc accounted for 35% (6/17 of the cases), but there was none in the females. They felt that QTc intervals shorter than 360 ms might entail some arrhythmic risk and are commonly seen in male patients with idiopathic VF. However, the 'short' QTc values are not rare among healthy adults, especially at slow heart rates. Our study showed that the high incidence of the short QTc value was in 30–40 years group (15.71%, 44/280). Gallaqher *et al* (13) reported a study of 12 500 cases of healthy males and found the incidence of QTc < 335 ms was 0.4% (54/12 500 cases), and that no one died after 7.9 ± 4.5 years of follow-up. However, other researchers such as Gollob *et al* (14) reported 62 cases of patients with short QTc, 75.4% were men, 35 cases of them (57.4%) suffered sudden cardiac death, or had been rescued from cardiopulmonary arrest, syncope and atrial fibrillation. Thus, the healthy people with short QTc might require regular follow-up, and the risk of death would be significantly increased if the sample

population was afflicted by other diseases. The incidence rate of children's short QTc was rarely reported in the current literatures. In this study, the incidence of children (< 18 years) was 5.89%, reaching to its low values in the 1–3 months and 3–6 months age groups, which were 0% and 0.76%, respectively. Pearl (15) has taken ECG on 781 healthy children from 10–18 years of age. They found that the QTc intervals were significantly ($p < 0.0005$) greater for each age group over 14 years of age. The QTc interval varied inversely with age and directly with heart rate. In our study, the incidence of the short QTc interval in younger than 6 months groups was low, so we deduced that the low incidence of the short QTc values was correlated with the higher average heart rates of younger babies. Rijinbeek *et al* (9) recruited 1912 children aged from 11 days to 16 years to record their ECG, and taken the 2nd percentiles as the lower limits of normal. In their study, they found that the lower QTc limits of 1–3 months group and 3–6 months group were higher than those of the other age groups, and that the values were 396 and 391 ms, respectively, which were consistent with our study's findings.

Antelmi *et al* (16) conducted a test of heart rate variability in different age groups (< 19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, ≥ 60 years), analysing the influence of age on autonomic nerve function. It was discovered that all time- and frequency-domain indexes including low frequency (LF), very low frequency, the standard deviation of average value of normal heartbeats in all 5-min sections, high frequency (HF), root mean square of the successive differences between normal adjacent heartbeat, and the number of heartbeat interval more than 50 ms (pNN50) were decreased significantly with age until the fourth decade of life and decreased non-significantly in the older age groups. However, the ratio of LF/HF increased with age in the group 20–50 years. This indicated that the tension of sympathetic nerve and parasympathetic nerve attenuated with the augmentation of age, of which the activity of the parasympathetic nerve reduced more remarkably, and the age group 30–39 years was the most significant. In this study, the incidence of short QTc reached its maximum in the age groups (18–30 years, 30–40 years, 40–50 years), which was 15.09% (35/232 of the cases), 15.71% (44/280 of the cases) and 13.11% (32/244 of the cases) respectively, of which the group 30–40 years was the most remarkable. Therefore, we deduced that it was the vagus that reduced more intensively, resulting in the highest incidence of the short QT. The QT interval is one of the most sensitive indexes that reflect the state of the local cardiac muscle repolarization.

Prolonged QT interval was related to myocardial electrical activity dyssynchrony and myocardial cell extension. Any factor causing the outflow of potassium ions weakened or calcium influx strengthened could the prolong action potential duration. There are many more studies about the drug that caused QT interval lengthening at present, showing that the most common cause of it was the fast delayed rectifier potassium current being affected (17). The incidence of long QTc in this study was 3.16%. The incidence of long QTc had no remarkable difference in all the age groups of the children, and decreased rapidly in the adults, reaching its trough in the age groups 18–30 years and 30–40 years, which were 0.86% and 0.71%, respectively. QTc extended was related to the sudden infant death syndrome or the risk of babies' life danger (18). Schwartz *et al* (19) studied 44 596 cases of infants aged from 12 days to 25 days, and found that the incidence of long QTc was 11.85%. A total of 28 cases of those newborn infants whose QTc was longer than 470 ms had gene tests, and of them 12 cases had gene mutation of LQTS. In the 28 cases of newborn infants whose QTc was between 460 and 470 ms, 12 cases of them had conducted DNA tests and 4 of them had the gene mutation of long QTc syndrome. In our study, the incidence of infants aged 1 month was 3.07%, the difference might due to the wider age range and ethnic differences. It reminded us that for the newborn infants' long QT interval, especially those longer than 470 ms, we needed to make a detailed inquiry of their family history and made the genetic diagnosis of LQTS. In this study, the incidence of children was 2.34%, and there was no statistically significant difference between males and females. This finding is similar to that of Dickinson (20). Pearl (15) reported 781 cases of healthy children aged from 10 to 18 years. The incidence of their long QT interval was 2.3%, of which the females' incidence was 1.9% and the males' incidence was 2.5%. There was no statistically significant difference between the genders ($p > 0.05$). In this study, the occurrence rate of the long QTc in the age groups of 8–10 years and 12–18 years was 1.42% and 2.23%, respectively, as they were in Pearl's report.

In our study, the incidence of the adults was 4.72%. Anttonen *et al* (12) had made a follow-up of 10 822 cases of people of middle age. The incidence of QTc longer than 450 ms was 6.5%, and for various reasons, the cardiovascular mortality in the people with long QTc

(longer than 450 ms) had significant difference compared with the people with normal QTc and short QTc (56.76% *vs* 51.8% *vs* 37.2%, $p < 0.05$). Therefore, the people of middle age needed regular follow-up to prevent cardiovascular events. Aggarwal *et al* (21) carried out a 1-year retrospective study of 384 cases of syncope patients caused by various reasons. All the patients had excluded atrial fibrillation, left bundle branch block, cardiac pacemaker and cardioverter-defibrillator installed. The QTc > 440 ms had been regarded as QTc extension, and the endpoint event of the research was death. After 30 months of follow-up, 58 cases of the patients died (16%), and the mortality was much higher than the group of normal QTc (22% *vs* 11%, $p < 0.01$). Ages over 65 years and QTc longer than 500 ms were the predictive markers of mortality of the syncope patients. In this study, the incidence of long QTc gradually increased in the 50-year-old patients, reaching the maximum in the age groups 50–60 years, 60–70 years and 70–83 years, and was 7.89%, 9.06% and 14.06%, respectively. Therefore, for the older people, especially in the syncope people, we should pay close attention to the extension of QTc to prevent cardiovascular accident. For the aged, their cardiac structure and function are gradually getting worse. Some studies showed that the abnormal cardiac structure could also change the QT interval (22). The factors like left ventricular hypertrophy (23), myocardial infarction or myocardial ischaemia (24), abnormal electrolyte (like hypokalaemia, hypomagnesaemia, hypocalcaemia) (25) and diabetic ketoacidosis or ketosis might contribute to the extension of the QT interval (26). In addition, the neurohumoral systems relevant to cardiovascular regulation are affected by ageing. In the elderly, an exaggerated shift towards the sympathetic activity had been reported (27), and such sympathetic overactivity had been proved to be an important factor to cause the prolongation of the QT interval and the increase of the QT dispersion (28, 29). Hence, the imbalance of the sympathetic and parasympathetic tones in the elderly may be another explanation for the increased QT interval. However, the patients would still need to take tests of ECG, heart Doppler ultrasound and electrolyte regularly in order to discover the symptoms early, so as to prevent cardiovascular events as the QT interval extend progressively.

CONCLUSION

The short and long QTc intervals existed in healthy people, and the high incidence of short QTc was in the patients aged 18–40 years. The high incidence of the long QTc was in the patients aged over 50 years. This might be because the activity of the sympathetic nerve and the parasympathetic nerve changed with age. As for these periods of age, we need to follow up high-risk people (*eg*, syncope, palpitation, metabolism disorder, and so on) with ECG.

ACKNOWLEDGEMENTS

The work is supported by the grants from the National Science Technology Support Plan Projects of 'Hunan Province Natural Science Foundation (13JJ5014)', 'Issue of Hunan Provincial Department of Public Health (B2013-013)', and '2020 Hunan Province Clinical Medical Technology Innovation Guidance Project (2020SK53405)'.

REFERENCES

1. Moss AJ. The QT interval and torsade de pointes. Drug Saf 1999; **21(Suppl 1):** 5–10.
2. Postema PG, Wilde AA. The measurement of the QT interval. Curr Cardiol Rev 2014; **10:** 287–94.
3. 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.
4. Williams ES, Thomas KL, Broderick S, Shaw LK, Velazquez EJ, Al-Khatib SM et al. Race and gender variation in the QT interval and its association with mortality in patients with coronary artery disease: results from the duke databank for cardiovascular disease. Am Heart J 2012; **164:** 434–41.
5. Bazzett HC. An analysis of the time-relations of electrocardiograms. Heart 1920; **7:** 353–67.
6. Bruno RM, Ghiadoni L, Seravalle G, Dell'oro R, Taddeis S, Grassi G. Sympathetic regulation of vascular function in health and disease. Front Physiol 2012; **3:** 284.
7. Smith AH, Norris KJ, Roden DM, Kannankeril PJ. Autonomic tone attenuates drug induced QT prolongation. Cardiovasc Electrophysiol 2007; **18:** 960–4.
8. Lenard Z, Studinger P, Mersich B, Kocsis L, Kollai M. Maturation of cardiovagal autonomic function from childhood to young adult age. Circulation 2004; **110:** 2307–12.
9. Rijinbeek PR, Witsenburg M, Schrama E, Hess J, Kors JA. New normal limits for the paediatric electrocardiogram. Eur Heart J 2001; **22:** 702–11.
10. Viskin S, Zeltser D, Ish-Shalom M, Katz A, Glikson M, Justo D et al. Is idiopathic ventricular fibrillation a short QT syndrome? Comparison of QT intervals of patients with idiopathic ventricular fibrillation and healthy controls. Heart Rhythm 2004; **1:** 587–91.
11. Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. Part IV: the ST segment, T and U waves, and the QT interval. J Am Coll Cardiol 2009; **53:** 982–91.
12. Anttonen O, Junttila MJ, Rissanen H, Reunaen A, Viltasal M, Huikuri HV. Prevalence and prognostic significance of short QT interval in a middle-aged finish population. Circulation 2007; **116:** 714–20.
13. Gallaqher MM, Maqliano G, Yap YG, Padula M, Morgia V, Postorino C et al. Distribution and prognostic significance of QT intervals in the lowest half centile in 12012 apparently healthy persons. Am J Cardiol 2006; **98:** 933–5.
14. Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. J Am Coll Cardiol 2011; **57:** 802–12.
15. Pearl W. Effects of gender, age and heart rate on QT intervals in children. Pediatr Cardiol 1996; **17:** 135–6.

16. Antelmi I, de Paula RS, Shinzato AR, Peres CA, Mansur AJ, Grupi CJ. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. Am J Cardiol 2004; **93:** 381–5.
17. Moric-Janiszewska E, Gloqowska-Liqus J, Paul-Samojedny M, Mrkievicz-Loskot G, Szydlowski L. Age-and sex-dependent mRNA expression of KCNQ1 and HERG in patients with long QT syndrome type 1 and 2. Arch Med Sci 2011; **7:** 941–7.
18. Yoldi A, Sena F, Gutierrez L. Prolongation of the QT interval and the sudden infant death syndrome. N Engl J Med 1998; **339:** 1162–3.
19. Schwartz PJ, Stramba-BedialeM, Crotti L, Pedrazzini M, Besana A, Bosi G, et al. Prevalence of the long QT syndrome. Circulation 2009; **120:** 1761–7.
20. Dickinson DF. The normal ECG in childhood and adolescence. Heart 2005; **91:** 1626–30.
21. Aggarwal A, Sherazi S, Levitan B, Lakshmandoss U, Choudhary N, Shah A et al. Corrected QT interval as a predictor of mortality in elderly patients with syncope. Cardiol J 2011; **18:** 395–400.
22. Levine E, Rosero SZ, Budzikowski AS, Moss AJ, Zareba W, Daubert JP. Congenital long QT syndrome: considerations for primary care physicians. Cleve Clin J Med 2008; **75:** 591–600.
23. Jouven X, Hagege A, Charron P, Carrier L, Dubourg O, Langlard JM et al. Relation between QT duration and maximal wall thickness in familial hypertrophic cardiomyopathy. Heart 2002; **88:** 153–7.
24. Schuchert A, Maas R, Kretzschmar C, Behrens G, Kratzmann I, Meinertz T. Diagnostic yield of external electrocardiographic loop recorders in patients with recurrent syncope and negative tilt table test. Pacing Clin Electrophysiol 2003; **26:** 1837–40.
25. Diercks DB, Shumaik GM, Harrigan RA, Brady WJ, Chan TC. Electrocardiographic manifestations: electrolyte abnormalities. J Emerg Med 2004; **27:** 153–60.
26. Kuppermann N, Park J, Glatter K, Marcin JP, Glaser NS. Prolonged QT interval corrected for heart rate during diabetic ketoacidosis in children. Arch Pediatr Adolesc Med 2008; **162:** 544–9.
27. Pfeifer MQ, Weinberg CR, Cook D, Best JD, Reenan A, Halter JB. Differential changes of autonomic nervous system function with age in man. Am J Med 1983; **75:** 249–58.
28. Guzman CE, Sanchez GM, Marquez MF, Hermosillo AG, Cardenas M. Differences in heart rate variability between cardioinhibitory and vasodepressor responses to head-up tilt table testing. Arch Med Res 1999; **30:** 203–11.
29. Loo SSS, Mathias CJ, Sutton MJ. QT interval and dispersion in primary autonomic failure. Heart 1996; **75:** 498–501.