Journal of Cardiology Cases 7 (2013) e117–e118

Contents lists available at www.sciencedirect.com

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Editorial

Is exercise-related QT interval shortening with a peaked T wave a specific electrocardiographic finding of pheochromocytoma?

Keywords:
Short QT syndrome
Long QT syndrome
Pheochromocytoma

The QT interval is an indirect scale of the time between ventricular depolarization and repolarization. Both markedly-abnormal long and short QT intervals are associated with an increased risk for sudden cardiac death due to life-threatening ventricular arrhythmia [1]. Long QT syndrome (LQTS) is characterized by prolonged QT interval on the surface electrocardiogram (ECG) and is associated with malignant arrhythmia leading to syncope, cardiac arrest, and sudden death [2]. LQTS can be subclassified into congenital and acquired forms. Genetic testing can identify a mutation in 50–75% of clinically affected patients with congenital LQTS, as well as some patients with acquired LQTS [3]. Thirteen genetic forms of LQTS have been described, and the most prevalent forms are LQT1 and LQT2 (due to mutations in potassium channels), and LQT3 (due to a sodium channel mutation) [1,4]. The acquired form of LQTS is more common than the congenital form; risk factors include use of QT-prolonging drugs, hypokalemia, bradycardia, and genetic variations in ion channel genes [5,6].

Short QT syndrome (SQTS) is characterized by abbreviated QT intervals and an increased susceptibility to arrhythmia and sudden death [7]. We analyzed 12,149 ECGs that had been recorded at our hospital for cardiac examination and demonstrated that the QTc intervals of 2 standard deviations below the mean were 354 ms in males and 364 ms in females, respectively [8]. Therefore, QTc <350 ms for males and 360 ms for females should be considered a short QT interval. The hereditary short QT syndrome is a genetic syndrome and five different genes encoding the potassium and calcium channels have been implicated in the pathogenesis of SQTS [9–12]. Gain of function mutations in patients in the *KCNH2* [9], *KCNQ1* [10], and *KCNJ2* [11] genes generate SQT1, SQT2, and SQT3 forms of SQTS. Loss of function missense mutations of the *CACNA1C* [12] and *CACNB2* [12] genes encoding the α1 and β2b subunits of the L-type calcium channel give rise to SQT4 and SQT5, respectively. Meanwhile, several conditions are known as secondary causes of short QT interval: hyperkalemia, hypercalcemia, hyperthermia, acidosis, effect of catecholamine or acetylcholine, chronic fatigue syndrome, use of digitalis, and abbreviation of QT interval related to activation of K_{ATP} current (Table 1) [13–16].

In this issue of *Journal of Cardiology Cases*, Gungor et al. report the case of a MEN2 male patient with exercise-related QT interval shortening with a peaked T wave [17]. The resting ECG showed normal QTc interval of 394 ms. However, the patient complained of dizziness and flushing during the treadmill exercise test and then showed QTc shortening of 309 ms and slowing of the heart rate of 56 bpm at second minute of recovery phase. Then, the patient was diagnosed as having MEN2 by endocrine examination and computed tomography scan, and underwent bilateral open adrenalectomy and total thyroidectomy. Histological findings showed bilateral pheochromocytoma and medullary thyroid carcinoma. Because previous study of the QT interval in recovery after exercise reported that the 2nd percentiles for the QTc using the Bazett formula at 2 min recovery was 393 ms [18], the patient's QTc interval at 2 min recovery was obviously short.

Several reasons were considered to explain the shortening of the QT interval with a peaked T wave after exercise in this patient. One explanation for this finding is augmentation of the sympathetic nerve activity. Several studies reported that the effect of catecholamine is one of the secondary causes of short QT interval [13,19,20]. Gungor et al. speculated that acute and massive catecholamine release caused a direct toxic effect on myocytes which resulted in these electrocardiographic changes [17]. The plasma catecholamine during exercise test in this patient was not measured but is thought to have increased, because a previous study reported that the post-exercise levels of epinephrine and the epinephrine/dopamine ratio were significantly higher in pheochromocytoma patients compared to healthy controls [21]. Reexamination of treadmill exercise test after bilateral adrenalectomy is helpful in confirming association between pheochromocytoma and short QT interval with a peaked T wave.

Table 1
Secondary causes of short QT interval in clinical practice.

Hyperkalemia
Hypercalcemia
Hyperthermia
Acidosis
Effect of catecholamine
Activation of K_{ACh}
Paradoxical shortening of the QT interval
Activation of K_{ATP}
Chronic fatigue syndrome
Digitalis

DOI of original article: http://dx.doi.org/10.1016/j.jccase.2012.10.012.

http://dx.doi.org/10.1016/j.jccase.2013.01.007

In contrast, conflicting studies were reported regarding whether catecholamine shortened absolute QT and corrected QT intervals: pheochromocytoma may induce QT prolongation [22], and exogenously administered epinephrine and isoproterenol cause minor QTc prolongation in normal healthy individuals [23]. The other explanation is deceleration-dependent shortening of QT interval [13,24]. Several reports showed patients with shortening of QT interval associated with a decrease in heart rate [24,25]. The patient in this study presented sinus bradycardia in recovery after exercise probably due to vasovagal reflex. Augmentation of the sympathetic nerve activity during exercise could cause excessive left ventricular contractions which resulted in vasovagal reflex thorough the left ventricular mechanoreceptor. Activation of the I_{KACh} caused by parasympathetic stimuli to the heart could be associated with a shortening of the action potential duration. Interestingly, a loss of function mutation in the *KCNJ5* gene which encodes the I_{KACh} channel subunit Kir3.4 was recently identified in congenital long QT syndrome [26]. Finally, it is important that gene analysis should be performed to test whether the patient has congenital short QT syndrome or not, and to detect mutations in the *RET* proto-oncogene which is a major gene responsible for MEN2.

Transient peaked T waves and shortening of QT interval during exercise stress testing in this issue are interesting findings and may provide an early clue for undiagnosed pheochromocytoma. It is necessary to elucidate the detailed mechanism and accumulate more pheochromocytoma patients with similar ECG changes, although careful monitoring of hemodynamics is needed when treadmill exercise test is performed for pheochromocytoma patients.

References

[1] Napolitano C, Bloise R, Monteforte N, Priori SG. Sudden cardiac death and genetic ion channelopathies: long QT, Brugada, short QT, catecholaminergic polymorphic ventricular tachycardia, and idiopathic ventricular fibrillation. Circulation 2012;125:2027–34.

[2] Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, Hall WJ, Weitkamp L, Vincent GM, Garson Jr A. The long QT syndrome. Prospective longitudinal study of 328 families. Circulation 1991;84:1136–44.

[3] Tester DJ, Will ML, Haglund CM, Ackerman MJ. Effect of clinical phenotype on yield of long QT syndrome genetic testing. J Am Coll Cardiol 2006;47:764–8.

[4] Liu L, Hayashi K, Kaneda T, Ino H, Fujino N, Uchiyama K, Konno T, Tsuda T, Kawashiri MA, Ueda K, Higashikata T, Shuai W, Kupershmidt S, Higashida H, Yamagishi M. A novel mutation in the transmembrane nonpore region of the *KCNH2* gene causes severe clinical manifestations of long QT syndrome. Heart Rhythm 2013;10:61–7.

[5] Roden DM, Viswanathan PC. Genetics of acquired long QT syndrome. J Clin Invest 2005;115:2025–32.

[6] Hayashi K, Shimizu M, Ino H, Yamaguchi M, Terai H, Hoshi N, Higashida H, Terashima N, Uno Y, Kanaya H, Mabuchi H. Probucol aggravates long QT syndrome associated with a novel missense mutation M124T in the N-terminus of HERG. Clin Sci (Lond) 2004;107:175–82.

[7] Gussak I, Brugada P, Brugada J, Wright RS, Kopecky SL, Chaitman BR, Bjerregaard P. Idiopathic short QT interval: a new clinical syndrome? Cardiology 2000;94:99–102.

[8] Funada A, Hayashi K, Ino H, Fujino N, Uchiyama K, Sakata K, Masuta E, Sakamoto Y, Tsubokawa T, Yamagishi M. Assessment of QT intervals and prevalence of short QT syndrome in Japan. Clin Cardiol 2008;31:270–4.

[9] Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, Menendez TM, Brugada J, Pollevick GD, Wolpert C, Burashnikov E, Matsuo K, Wu YS, Guerchicoff A, Bianchi F, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation 2004;109:30–5.

[10] Bellocq C, van Ginneken AC, Bezzina CR, Alders M, Escande D, Mannens MM, Baro I, Wilde AA. Mutation in the *KCNQ1* gene leading to the short QT-interval syndrome. Circulation 2004;109:2394–7.

[11] Priori SG, Pandit SV, Rivolta I, Berenfeld O, Ronchetti E, Dhamoon A, Napolitano C, Anumonwo J, di Barletta MR, Gudapakkam S, Bosi G, Stramba-Badiale M, Jalife J. A novel form of short QT syndrome (SQT3) is caused by a mutation in the *KCNJ2* gene. Circ Res 2005;96:800–7.

[12] Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, Guerchicoff A, Pfeiffer R, Oliva A, Wollnik B, Gelber P, Bonaros Jr EP, Burashnikov E, Wu Y, Sargent JD, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation 2007;115:442–9.

[13] Patel C, Yan GX, Antzelevitch C. Short QT syndrome: from bench to bedside. Circ Arrhythm Electrophysiol 2010;3:401–8.

[14] Naschitz J, Fields M, Isseroff H, Sharif D, Sabo E, Rosner I. Shortened QT interval: a distinctive feature of the dysautonomia of chronic fatigue syndrome. J Electrocardiol 2006;39:389–94.

[15] Gomes JA, Dhatt MS, Akhtar M, Carambas CR, Rubenson DS, Damato AN. Effects of digitalis on ventricular myocardial and His-Purkinje refractoriness and reentry in man. Am J Cardiol 1978;42:931–8.

[16] Garberoglio L, Giustetto C, Wolpert C, Gaita F. Is acquired short QT due to digitalis intoxication responsible for malignant ventricular arrhythmias? J Electrocardiol 2007;40:43–6.

[17] Gungor O, Ozeke O, Sayinalp S, Ertan C, Demir AD, Ilicin G, Ozer C. Exercise-related QT interval shortening with a peaked T wave in a boy with MEN 2 syndrome. J Cardiol Cases 2013;7:e93–6.

[18] Berger WR, Gow RM, Kamberi S, Cheung M, Smith KR, Davis AM. The QT and corrected QT interval in recovery after exercise in children. Circ Arrhythm Electrophysiol 2011;4:448–55.

[19] Chinushi M, Sato A, Iijima K, Suzuki K, Hiroshi F, Izumi D, Watanabe H, Kanae H, Aizawa Y. Exercise-related QT interval shortening with a peaked T wave in a healthy boy with a family history of sudden cardiac death. Pacing Clin Electrophysiol 2012;35:e239–42.

[20] Kawataki M, Kashima T, Toda H, Tanaka H. Relation between QT interval and heart rate. Applications and limitations of Bazett's formula. J Electrocardiol 1984;17:371–5.

[21] Telenius-Berg M, Adolfsson L, Berg B, Hamberger B, Nordenfelt I, Tibblin S, Welander G. Catecholamine release after physical exercise. A new provocative test for early diagnosis of pheochromocytoma in multiple endocrine neoplasia type 2. Acta Med Scand 1987;222:351–9.

[22] Paulin FL, Klein GJ, Gula LJ, Skanes AC, Yee R, Krahn AD. QT prolongation and monomorphic VT caused by pheochromocytoma. J Cardiovasc Electrophysiol 2009;20:931–4.

[23] Magnano AR, Talathoti N, Hallur R, Bloomfield DM, Garan H. Sympathomimetic infusion and cardiac repolarization: the normative effects of epinephrine and isoproterenol in healthy subjects. J Cardiovasc Electrophysiol 2006;17:983–9.

[24] Gussak I, Liebl N, Nouri S, Bjerregaard P, Zimmerman F, Chaitman BR. Deceleration-dependent shortening of the QT interval: a new electrocardiographic phenomenon? Clin Cardiol 1999;22:124–6.

[25] Takahashi N, Ito M, Ishida S, Nakagawa M, Hara M, Saikawa T, Sakata T. Paradoxically shortened QT interval after a prolonged pause. Pacing Clin Electrophysiol 1998;21:1476–9.

[26] Yang Y, Liang B, Liu J, Li J, Grunnet M, Olesen SP, Rasmussen HB, Ellinor PT, Gao L, Lin X, Li L, Wang L, Xiao J, Liu Y, Zhang S, et al. Identification of a Kir3.4 mutation in congenital long QT syndrome. Am J Hum Genet 2010;86:872–80.

Kenshi Hayashi (MD, PhD)*
Tetsuo Konno (MD, PhD)
Hidekazu Ino (MD, PhD)
Masakazu Yamagishi (MD, PhD)
Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8640, Japan

* Corresponding author. Tel.: +81 76 265 2254; fax: +81 76 234 4251.
E-mail address: kenshi@med.kanazawa-u.ac.jp (K. Hayashi)

21 January 2013