Original Article

Iran J Pediatr
Dec 2013; Vol 23 (No 6), Pp: 687-692

Cardiac Repolarization Changes in the Children with Breath-Holding Spells

Hamid Amoozgar[1], MD; Fazl Saleh[1], MD; Nahal Farhani[1], MD; Mohammad Rafiei[2], MD; Soroor Inaloo[2], MD; Ali-Akbar Asadipooya[2], MD

1. Department of Pediatrics, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran
2. Department of Neurology, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

Received: *Mar 30, 2013*; Accepted: *Jul 06, 2013;* First Online Available: *Nov 22, 2013*

Abstract

Objective: Breath-holding spells are known as benign attacks, frequencies of which decrease by the development of the autonomic nervous system. The present study aims to compare the electrocardiographic repolarization in children with breath-holding spells.

Methods: In this study, QT dispersion, QTc dispersion, T peak to T end dispersion, and P wave dispersion of the twelve-lead surface electrocardiography of fifty children who had breath-holding spells were measured and compared with normal children from April 2011 to August 2012.

Findings: Forty-four (88%) patients had cyanotic spells, while 6 (12%) had pallid spells. QTc dispersion was increased in the patients with breath-holding spells (148.2±33.1) compared to the healthy children (132±27.3) and the difference was statically significant (P=0.01). Meanwhile, no statistically significant differences were observed between the patients and the control subjects regarding the other parameters (P>0.05).

Conclusion: QTc dispersion was significantly increased in the patients with breath-holding spells compared to normal children and this is a sign of cardiac repolarization abnormality as well as the increased risk of cardiac arrhythmia in patients with breath-holding spells.

Iranian Journal of Pediatrics, Volume 23 (Number 6), December 2013, Pages: 687-692

Key Words: Breath-Holding Spell; Arrhythmia; Cardiomyopathy; QT Interval Dispersion; Autonomic Dysfunction

Introduction

Breath-holding spell is a common clinical event. Each attack starts with a brief crying period after a minimal injury or reprimand followed by a prolonged expiration. Some children may also experience loss of consciousness[1,2]. Based on the skin color change during the attacks, breath holding spell has two types: pallid spells and cyanotic spells; however, some children may experience mixed type attacks[3]. Overall, the cyanotic type is more common and its prevalence to pallid type is 3 to 1. Although these attacks were previously considered as benign episodes spontaneously resolving in the children between 6 and 8 years old, recent studies have shown that many of these patients will develop syncope attacks in the future[4].

The pathogenesis of breath holding spells are not well understood, but some studies suggest that imbalance between sympathetic and para-sympathetic activity could be responsible for the manifestations[3,4]. Bradycardia and asystole are most likely mediated by excessive para-

*** Corresponding Author;**
Address: Department of Pediatrics, Namazi Hospital, 7193711351 Shiraz, Iran
E-mail: amozgah@sums.ac.ir

sympathetic tone which then results in brain hypoperfusion, seizure, and loss of consciousness[3].

The autonomic nervous system is an important modulator of ventricular repolarization and arrhythmia vulnerability. Among different predictors of ventricular repolarization, increased QT interval, QT dispersion, T peak to T end interval dispersion, and their relationship with different cardiac and autonomic disorders, such as cardiomyopathies, ischemic heart disease, migraine, familial dysautonomia and syncope have been investigated in many studies[1,5-7]. These simple and noninvasive electrocardiographic (ECG) findings are considered to reflect abnormal ventricular repolarization which is associated with arrhythmogenesis[6,7]. QT interval is closely related to ventricular repolarization[8]. In fact, QT dispersion reflects regional variations in ventricular repolarization. Several reports indicated that QT dispersion from 12-lead surface electrocardiogram provided an indirect measurement of the underlying non homogeneity of ventricular repolarization[9,10].

The terminal end of the QT interval, T wave peak to T end, represents the transmural dispersion of repolarization of ventricle and has been proposed as an indicator of ventricular arrhythmia. Some articles demonstrated that differences in the action potential of different myocardial layers lead to repolarization dispersion[11,12].

In addition, recent studies have used P wave dispersion as a parameter for the prediction of atrial arrhythmias in several disorders[13]. Increased P wave dispersion reflects the inhomogeneity and discontinuity of atrial conduction[14,15].

Recently, Akalin et al[16] demonstrated that QT dispersion increased in children with breath-holding spells and they suggested this finding justifies further investigation for rhythm abnormalities and autonomic dysfunction in this patient group.

To the best of our knowledge, T wave peak to T end dispersion and P wave dispersion have not been studied in the children who have breath holding spells. The present study aims to compare the electrocardiographic repolarization between children with breath-holding spells and normal controls.

Subjects and Methods

This prospective, case-control study was conducted in the pediatrics cardiology department of Namazi Hospital, Shiraz, Iran from April 2011 to August 2012. Informed parental consent was obtained for every child before recruitment into the investigation and the investigation was approved by the ethics committee of Shiraz University of Medical Sciences.

The patients were selected consecutively among children younger than 10 years old who had been referred to the pediatrics cardiology department after diagnosis of breath-holding spell by pediatric neurologist. The exclusion criteria of the study were any congenital heart disease, any CNS abnormalities, and any endocrine or nephrology disorder which could cause ECG changes. The patients' demographic data and the type as well as the pattern of the attacks were collected. At the same time, 50 healthy children less than 10 years old who had no history of cardiac, neurologic, endocrine and breath holding spell were recruited as control subjects.

The 12-lead surface electrocardiography was obtained from all the patients and the controls by the personnel without knowledge of children's clinical status. The recordings were made through a digital electrocardiogram machine (Alicia Diagnostics, Sanford, FL, USA). The digitally recorded electrocardiogram tracings were evaluated using a digital caliper in Corel draw graphic software (Ottawa, Canada). Magnification of the electrocardiogram made a fine determination of the measurement points. The onset of the P wave was defined as the junction between the isoelectric line and the start of the P wave deflection. Besides, the offset of the P wave was defined as the point where the final deflection of the P wave crossed the isoelectric line. The leads with unclear onset or offset of the P wave were excluded from the study. Then, the P wave dispersion was calculated according to its definition as the difference between P maximum duration and P minimum duration in 12-lead ECG[15].

QT intervals were measured from the onset of the QRS complexes to the end of the T waves. The end of the QT interval was defined as the intersection of a tangent to the steepest down slope of the dominant repolarization wave with

the isoelectric line. QT was measured in all 12 leads, and the longest was recorded as QT of the subject. QT dispersion (QTD) is defined as the difference between the longest and the shortest QT intervals on the surface ECG. For measuring QTc, the QT interval was corrected for heart rate using Bazett's formula (QTc=QT/square root of RR interval in s). The QTc dispersion was measured as the difference between the maximum and the minimum QTc intervals on the 12-lead surface ECGs[16].

For measuring T wave peak to T wave end interval, we measured the interval between the beginning of QT interval and the peak of the T wave and subtracted this interval from the QT interval. T wave peak to T end dispersion (TPE dispersion) is defined as the difference between the longest and the shortest T wave peak to T end intervals on the surface ECG. If the height or depth of the T wave was <1.5 mm or if the T wave was flat, its lead was excluded from the analysis[17].

Hemoglobin and mean corpuscular volume were measured in all patients to detect iron deficiency anemia. Iron deficiency anemia defined as having a hemoglobin level of <10.5 g/dl and mean corpuscular volume values of <75 fl.

All electrocardiogram measurements were done by a physician who was blinded to patient and control group.

The differences in ECG parameters, including QT dispersion, QTc dispersion, T wave peak to T end dispersion, and P wave dispersion, were compared between the two study groups using t-test. The data were expressed as mean±SD. Moreover, $P<0.05$ was considered as statistically significant.

Findings

The present study was conducted on 50 children (23 females and 27 males) between 6 and 84 (31.6±20.2) months with breath-holding spells. The control group (n=50) included 26 females and 24 males between 7 and 91 (33.1±21.7) months old ($P=0.7$). In the patients group, on the other hand, 44 (88%) children were suffering from cyanotic type of breath-holding spells, while 6 children were suffering from pallid spells.

As Table 1 depicts, the mean of the QTc dispersion in the patients was more than that in healthy children (148.2±33.1 milliseconds and 132±27.3 milliseconds, respectively) and the difference was statically significant ($P=0.01$). Meanwhile, no statistically significant difference was found regarding the other ECG parameters, including P wave dispersion, QT dispersion, and T wave peak to T wave end dispersion ($P>0.05$). The difference in QTc dispersion of the patients and normal children is also depicted in Fig. 1.

The study findings revealed no statistically significant difference between the children who had cyanotic spells and those who had pallid spells concerning P wave dispersion, QT dispersion, QTc dispersion, and T peak to T end dispersion despite slightly higher QT dispersion, QTc dispersion, and T peak to T end dispersion values in the patients who had cyanotic spells.

Mean hemoglobin in patient group was 9.61±3.12. According hemoglobin level of <10.5 g/dl and mean corpuscular volume values of <75 fl, 32 (62%) patients had anemia. There was no statistically significant difference between QT, QT dispersion, T peak to end and P dispersion of anemic and non anemic patients ($P>0.05$).

Table 1: Comparison of QT dispersion, P dispersion, QTc dispersion, and T wave peak to T end dispersion between the patients and the control group

Variable		Mean (millisecond)	Standard deviation	*P.* value
QT dispersion	Control group	48.9	16.8	0.74
	Patients	47.8	15.2	
P dispersion	Control group	38.9	13.1	0.28
	Patients	35.9	13.4	
QTc dispersion	Control group	132	27.3	0.01
	Patients	148.2	33.1	
TPE dispersion	Control group	55	20.1	0.06
	Patients	47	20.3	

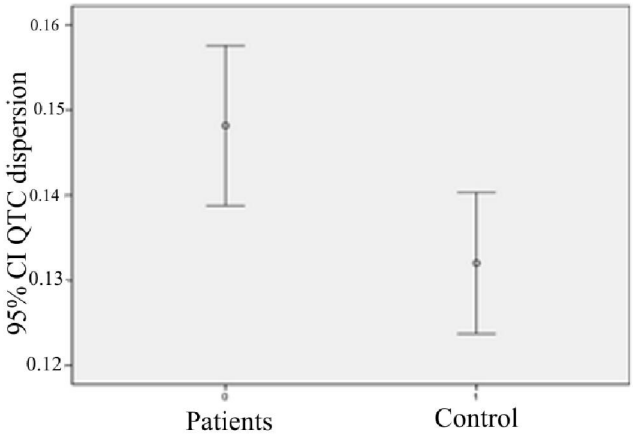

Fig. 1: Comparison of QTc dispersion between the patients with breath-holding spell and the control group

Discussion

Breath-holding spells are benign and common clinical conditions. The prevalence of this condition is reported as 4% to 27% of the children between six months and six years old in different studies[18]. In a study by Olsen et al[19], 30.6% of the children who had breath holding spells in childhood suffered from fainting spells and 29.4% of these children had concentration problems in the long term. A familial tendency to epilepsy was also reported in this study. In another study, Di Mario et al[4] followed the children with breath-holding spells for long term complications and reported syncopal attacks and hypoxic convulsion in 12.6% and 15.7% of the children, respectively.

The pathogenesis of breath holding spells are not well understood, but some studies suggest that imbalance between sympathetic and para-sympathetic activity could be responsible for the manifestations[3,4]. Bradycardia and asystole are most likely mediated by excessive para-sympathetic tone which then results in brain hypoperfusion, seizure, and loss of consciousness [3,15]. Iron deficiency anemia is more prevalent among the children with breath-holding spells compared with other normal children and appears to contribute to the breath-holding spells with three underlying mechanisms. First, anemia itself causes hypoxia in vital organs, including the heart and the nervous system. Second, hypoxia which is sensed by carotid body results in activation of cardiovascular reflexes which play a major role in altered autonomic balance[20]. Finally, iron plays a vital role in providing Tyrosine Hydroxylase enzyme for catecholamine synthesis[21]. Although Iron deficiency anemia is more prevalent among the children with breath holding spells, autonomic dysfunction is considered as the main pathogenesis of this clinical entity. In our study also 63% of patients had anemia but there was no statistically significant correlation between anemia and repolarization changes.

In a study performed by Anil et al[22], abnormality of autonomic reflexes, including increased basal heart rate, increased diastolic blood pressure, and abnormal pupillary reactions, suggested a subtle underlying generalized autonomic dysfunction in the children with breath-holding spells.

Autonomic dysfunction affects intra- and interatrial conduction resulting in inhomogeneity and discontinuity in atrial conduction system. P wave dispersion (the difference between the longest and the shortest P wave duration recorded from multiple surface ECG leads) is a noninvasive method for assessment of the risk for atrial fibrillation which is the result of inhomogeneity and discontinuity in atrial conduction. Imamoglu et al[23] reported that P wave dispersion was increased in the children with diabetes type 1 (aged 14.2±4.8 years). Also, Simsek et al[24] reported prolongation of P wave dispersion in adult patients with iron deficiency anemia because of autonomic dysfunction and tissue hypoxia. However, the findings of the current study revealed no statistically significant changes in P wave dispersion in the children with breath

holding spells compared to the normal children. This inconsistency with the above-mentioned studies maybe explained by the severity of the autonomic system damage in diabetic patients in comparison to the children with breath holding spells. The age of the patients in those two studies which was profoundly higher compared to the age of our patients, and probably the underlying mechanisms impaired the autonomic system function in these three diseases.

A number of ECG markers of ventricular repolarization have been reported to identify the patients who are at high-risk for development of ventricular arrhythmias[9-11]. Among different predictors, increased QT dispersion, QTc dispersion, and T peak to T end dispersion are considered as the markers that reflect the abnormal ventricular repolarization which is associated with arrhythmogenesis[1,5].

QT dispersion (defined as the difference between maximal and minimal QT interval duration in all measurable ECG leads) is a method for determining myocardial repolarization inhomogeneities. The exact relationship between the heart rate and ventricular recovery dispersion is still unknown. Some studies demonstrated that QT dispersion was increased with premature beats[25,26].

Akalin et al[16] measured QT dispersion and QTc dispersion of 43 children aged 22.7±17.7 months with breath holding spells and compared them with the same ECG markers of 25 normal children matched to the patients regarding their age and sex. They demonstrated that QT dispersion and QTc dispersion were significantly increased in the children with breath holding spells compared to the normal subjects.

In the present study, we calculated both QT dispersion and QTc dispersion and found that QTc dispersion had significantly increased in the patients with breath-holding spells compared to the control subjects; however, no statistically significant changes were observed in QT dispersion of the patients and the control subjects. These results may suggest that QTc dispersion is a more sensitive predictor of ventricular repolarization inhomogeneity in comparison to QT dispersion. By correcting the QT interval using Bazett formula, respiratory sinus arrhythmia which is more prominent in the children with breath holding spells will not affect the QT interval and may not affect the QT dispersion, as well.

Furthermore, endocardial, epicardial, and M cells are three distinct electrophysiological cell types that have significant differences in the time course of repolarization. The T wave on the surface ECG results from transmural voltage gradient of these three types of cells and T peak to T end interval provides transmural dispersion of repolarization. Although this theory is proven by evaluation of left ventricular wedge preparations which only assess the transmural voltage gradients, it is not clear whether the T peak to T end interval is actually a reflection of transmural dispersion of repolarization in the living hearts[27,28]. Nevertheless, a large number of studies have shown that T peak to T end interval on the surface ECG is a helpful marker for prediction of the risk for the development of life-threatening arrhythmias[29-32]. In this study, we also measured T wave peak to T end dispersion and compared this parameter in the healthy children and the children suffering from breath holding spells and the results demonstrated no statistically significant differences between these two groups.

The main limitation of this study was its limited follow up period. It is highly probable that by further follow up and cardiac evaluation of these patients, more significant abnormal ECG findings will be found.

Conclusion

QTc dispersion was significantly increased in the patients with breath-holding spells compared to the normal children and this is a sign of cardiac repolarization changes as well as increased risk of cardiac arrhythmia in breath-holding spells.

Acknowledgment

Research Improvement Center of Shiraz University of Medical Sciences, and Ms. A. Keivanshekouh are appreciated for improving the use of English in the manuscript. This work was financially supported by vice chancellery of research of Shiraz University of Medical Sciences.

Conflict of Interest: None

References

1. Higham PD, Campbell RW. QT dispersion. *Br Heart J* 1994;71(6):508-10.
2. Dalton R, Boris NW. Disruptive behavioral disorders. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, Zitelli BJ, Davis HW (eds). Nelson Textbook of Pediatrics. 18th ed. Philadelphia: Saunders Elsevier; 2007; Pp: 1226-9.
3. DiMario FJ Jr, Burleson JA. Autonomic nervous system function in severe breath-holding spells. *Pediatr Neurol* 1993;9(4):268-74.
4. DiMario FJ Jr. Prospective study of children with cyanotic and pallid breath-holding spells. *Pediatrics* 2001;107(2):265-9.
5. Melek IM, Seyfeli E, Duru M, et al. Autonomic dysfunction and cardiac repolarization abnormalities in patients with migraine attacks. *Med Sci Monit* 2007;13(3):RA 47-9.
6. Amoozgar H, Hosseiniasl M. T-Peak to T-End abnormality in pediatric patients with syncope. *Iran J Pediatr* 2012;22(3):385-91.
7. Glickstein JS, Axelrod FB, Friedman D. Electrocardiographic repolarization abnormalities in familial dysautonomia: an indicator of cardiac autonomic dysfunction. *Clin Auton Res* 1999;9(2): 109-12.
8. Bednar MM, Harrigan EP, Anziano RJ, et al. The QT interval. *Prog Cardiovasc Dis* 2001;43(5 Suppl 1):1-45.
9. Mkparu FO. QT dispersion: proposed technique for optimal risk stratification. *Am J Cardiol* 1995; 76(17):1323.
10. Linker NJ, Colonna P, Kekwick CA, et al. Assessment of QT dispersion in symptomatic patients with congenital long QT syndromes. *Am J Cardiol* 1992; 69(6):634-8.
11. Antzelevitch C, Sun ZQ, Zhang ZQ, et al. Cellular and ionic mechanisms underlying erythromycin-induced long QT intervals and torsade de pointes. *J Am Coll Cardiol* 1996;28(7):1836-48.
12. Yamaguchi M, Shimizu M, Ino H, et al. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. *Clin Sci (Lond)* 2003;105(6):671-6.
13. Dilaveris PE, Gialafos EJ, Sideris SK, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. *Am Heart J* 1998;135(5 Pt 1):733-8.
14. Dilaveris PE, Gialafos EJ, Andrikopoulos GK, et al. Clinical and electrocardiographic predictors of recurrent atrial fibrillation. *Pacing Clin Electrophysiol* 2000;23(3):352-8.
15. Tsikouris JP, Klugger J, Song J, et al. Changes in p-wave dispersion and p wave duration after open heart surgery are associated with peak incidence of atrial fibrillation. *Heart Lung* 2001;30(6):466-71.
16. Akalin F, Turan S, Guran T, et al. Increased QT dispersion in breath-holding spells. *Acta Paediatr* 2004;93(6):770-4.
17. Surawicz B, Knobel SB. Long QT: good, bad or indifferent? *J Am Coll Cardiol* 1984;4(2):398-413.
18. Lombroso CT, Lerman P. Breath holding spells (cyanotic and pallid infantile syncope). *Pediatrics* 1967;39(4):563-81.
19. Olsen AL, Mathiasen R, Rasmussen NH, et al. Long-term prognosis for children with breath-holding spells. *Dan Med Bull* 2010; 57(11):A4217.
20. Lahiri S, Roy A, Baby SM, et al. Oxygen sensing in the body. *Prog Biophys Mol Biol* 2006;91(3):249-86.
21. Tsiftsoglou AS, Tsamadou AI, Papadopoulou LC. Heme as key regulator of major mammalian cellular functions: molecular, cellular, and pharmacological aspects. *Pharmacol Ther* 2006;111(2):327-45.
22. Anil BG, Nedunchezian K, Jayanthini V, et al. Breath holding spells: evaluation of autonomic nervous system function. *Indian Pediatr* 2005;42(9):923-7.
23. Imamoglu EY, Oztunc F, Eroglu AG, et al. Dispersion of the P wave as a test for cardiac autonomic function in diabetic children. *Cardiol Young* 2008; 18(6):581-5.
24. Simsek H, Gunes Y, Demir C, et al. The effects of iron deficiency anemia on p wave duration and dispersion. *Clinics (Sao Paulo)* 2010;65(11):1067-71.
25. Dabrowski A, Kramarz E, Piotrowicz R, et al. Predictive power of increased QT dispersion in ventricular extrasystoles and in sinus beats for risk stratification after myocardial infarction. *Circulation* 2000;101(14):1693-7.
26. Day CP, McComb JM, Campbell RW. QT dispersion in sinus beats and ventricular extrasystoles in normal hearts. *Br Heart J* 1992;67(1):39-41.
27. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long QT syndrome. *Circulation* 1998;98(18): 1928-36.
28. Fish JM, Di Diego JM, Nesterenko VV, et al. Epicardial activation of left ventricular wall prolongs QT interval and transmural dispersion of repolarization: implications for biventricular pacing. *Circulation* 2004;109(17):2136-42.
29. Antzelevitch C, Shimizu W, Yan GX, et al. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. *J Cardiovasc Electrophysiol* 1999;10(8):1124-52.
30. Emori T, Antzelevitch C. Cellular basis for complex T waves and arrhythmic activity following combined I(Kr) and I(Ks) block. *J Cardiovasc Electrophysiol* 2001;12(12):1369-78.
31. Watanabe N, Kobayashi Y, Tanno K, et al. Transmural dispersion of repolarization and ventricular tachyarrhythmias. *J Electrocardiol* 2004; 37(3):191-200.
32. Milberg P, Reinsch N, Wasmer K, et al. Transmural dispersion of repolarization as a key factor of arrhythmogenicity in a novel intact heart model of LQT3. *Cardiovasc Res* 2005;65(2):397-404.