Journal of Electrocardiology 55 (2019) 116–119

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

Ventricular repolarization changes in children with breath holding spells

Melis Akpinar [a,*], Meric Ocal [a], Ahmet Irdem [b]

[a] Department of Pediatrics, Okmeydani Training and Research Hospital, Istanbul, Turkey
[b] Department of Pediatric Cardiology, Okmeydani Training and Research Hospital, Istanbul, Turkey

ARTICLE INFO

Keywords:
Breath holding spells
Ventricular repolarization

ABSTRACT

Objective: Breath holding spells is a non-epileptic paroxysmal disease which is frequently seen in childhood. In this study, we aimed to investigate electrocardiographic atrial conduction and ventricular repolarization changes in children with breath holding spells.
Materials and methods: We reviewed the electrocardiograms of 58 patients with breath holding spells who admitted to SBU Okmeydanı SUAM Pediatric Cardiology Clinic between November 2018 and February 2019. QT, QTc (calculated with Bazett formula), T peak-end (Tp-e), QT dispersion (QTd), QTc dispersion (QTcd), Tp-e/QT ratio, Tp-e/QTc ratio, JT interval, JTc (calculated with Bazett formula), Tp-e/JT ratio, Tp-e/JTc ratio and P dispersion (Pd) were measured and compared with the control group of 44 healthy children.
Results: In the control and the case groups, mean QTd was 19.86 ms and 38.57 ms, QTcd was 28.34 ms and 58.03 ms, Tp-e/QT ratio was 0.16 and 0.26, Tp-e/QTc ratio was 0.11 and 0.17, JT interval was 204.09 ms and 224.52 ms, JTc value was 290.00 ms and 333.72 ms, Tp-e/JT ratio was 0.23 and 0.35, Tp-e/JTc ratio was 0.16 and 0.24, Pd was 29.32 ms and 40.53 ms respectively. Differences between two groups were statistically significant ($p < 0{,}001$).
Conclusion: QTd, QTcd, Tp-e, Tp-e/QT ratio, Tp-e/QTc ratio, JT, JTc, Tp-e/JT, Tp-e/JTc ratio and Pd were increased significantly compared to healthy children. Based on the results, ventricular repolarization and atrial conduction were affected in patients with breath holding spells. These patients may be under the risk of developing rhythm disorders.

Introduction

Breath holding spell is a non-epileptic paroxysmal disease which is frequently seen in childhood, with the prevalence of 5%. Although the etiology is not known, autonomic dysfunction and increased vagal tonus leading to cardiac arrest and cerebral anoxia are considered to play a role. The typical age of onset is 6–18 months, and it disappears towards the age of six with the maturation of autonomic system. Attacks start with a short crying after a minor trauma or an emotional stress and end with a longer period of expiration. Some children may experience unconsciousness. Based on changes in skin color during the spell, breath holding spells can be divided into three groups as cyanotic, pallid and mixed [1,2].

Although these attacks were previously considered as benign episodes spontaneously disappearing in children between 6 and 8 years old, recent studies have shown that many of these patients may develop arrhythmia and syncope attacks in their future life [3–6].

QT dispersion (QTd) is a non-invasive evaluation way of ventricular myocardium repolarization by electrocardiogram (ECG) and also shows the risk of severe ventricular arrhythmia and coronary artery disease. In different diseases such as cardiomyopathy, mitral valve prolapse, ischemic heart disease and renal insufficiency, QTd may increase the risk of arrhythmia and sudden death [7,8]. In a study, QTd was found to be statistically significantly increased in patients with spells [9], but in another study there was no difference in QT between healthy children and children with spells [10]. In another study, it was shown that breath holding spells may occur as the first symptom of children with long QT syndrome [11].

Abnormal ventricular repolarization is an important mechanism in malignant ventricular arrhythmias and cardiovascular mortality [12]. In addition to QTd, recent ECG indices such as T peak-end (Tp-e), Tp-e/QT ratio have emerged as markers of the transmural dispersion of repolarization [13–17]. The prolongation of the Tp-e interval and the increase in the Tp-e/QT ratio are associated with malignant ventricular arrhythmia in long QT syndrome, Brugada syndrome and hypertrophic cardiomyopathy [18,19].

The JT and JTc are more specific measurements of ventricular repolarization than QT and QTc by eliminating QRS duration variability. It appears to be a more useful predictor of repolarization abnormalities, and may be helpful to identify patients with LQTS who have borderline or normal QTc measurements on ECGs [20].

* Corresponding author.
E-mail address: melisakpinar1990@hotmail.com (M. Akpinar).

https://doi.org/10.1016/j.jelectrocard.2019.05.013
0022-0736/

There are few studies in the literature about these new indices in children with breath holding spells. Amoozgar et al. [21] demonstrated in their study that in children with breath holding spells QTcd increased, but there was no statistically significant difference in Tp-e and P wave dispersion (Pd).

In this study, we evaluated new ECG indices for abnormal ventricular repolarization and atrial conduction in children with breath holding spells.

Materials and methods

This study includes 58 children, 1 mo-old to 6 yr-old age, diagnosed with breath holding spell at Okmeydanı Training and Research Hospital Pediatric Cardiology Clinic, Istanbul, Turkey from November 2018 to February 2019. The patients had no additional disease and no drug use. Echocardiograms (ECO) and ECGs were taken from all children.

Electrocardiograms were performed at 12 lead, 25 mm/sec speed and 10 mm/mV calibration. The control group included 44 healthy children aged 1 mo-old to 6 yr-old age who were referred to the Pediatric Cardiology Clinic for regular checkups and had no abnormality in cardiac examination, ECG and ECO. The study was approved by the Ethics Committee of Okmeydanı Training and Research Hospital, Istanbul, Turkey.

Age, gender and weight information of the case and the control groups were recorded. In the ECGs, P, QRS, T wave, PR interval (from the beginning of the P wave to the beginning of the QRS complex), QT interval (from the beginning of the Q wave to the end of the T wave), QTc (calculated with Bazett formula), T peak-end (Tp-e, the interval between the peak and end of the T wave), QTd (QT dispersion; difference between the minimal and maximal QT intervals measured in all leads in each patient's ECG), QTcd (QTc dispersion; measured in all leads of ECG and calculated with Bazett formula) Pd (P dispersion; difference between the minimal and maximal P intervals measured in all leads in each patient's ECG), Tp-e/QT ratio, Tp-e/QTc ratio, JT interval (between the end of the S wave and end of the T wave), JTc (calculated with Bazett formula) Tp-e/JT ratio and Tp-e/JTc ratio were measured and compared with the control group. All the measurements were taken using magnification and a manual ruler by 2 observers blinded to the study. Intra- and interobserver variability for the measurements was determined as <5%. Measurements were not taken in ECG leads which have high artifacts and where the starting or finishing point of the waves could not be selected.

Statistical Package for Social Sciences (SPSS) 22.0 program was used for statistical analysis. Quantitative data were compared with "T-Test "and qualitative data were compared with" Chi-Square Test". $p < 0.05$ was considered as statistically significant.

Results

Out of 58 case group, 31 were female (53%) and out of 44 control group, 22 were female (50%). No statistically significant difference was found between the groups at gender comparison ($p = 0.73$).

The mean age in the case group was 20.82 ± 18.2 months (between 1 and 72 months) and the control group was 22.23 ± 18.5 months (between 1 and 72 months) and there was no statistically significant difference. ($p = 0.95$).

The mean weight was 11.94 ± 4.5 kg in the case group and 12 ± 9.5 kg in the control group and no statistically significant difference was observed between the groups ($p = 0.7$).

The mean heart rate was 138.02 ± 27.8 bpm in the case group and 125.07 ± 23.6 bpm in the control group with a statistically significant difference ($p = 0.015$).

No statistically significant difference was found between the case and the control group regarding the P, PR, QRS and T intervals in ECG measurements and the data are given in Table 1.

Table 1
P, PR, QRS and T intervals in the case and the control groups.[a]

	Case	Control	p value
P interval (ms)	84.31 ± 146	83.91 ± 17.5	0.90
PR interval (ms)	11,134 ± 157	116.64 ± 15.7	0.09
QRS interval (ms)	71.76 ± 74	69.05 ± 10.1	0.12
T interval (ms)	166.9 ± 37.8	159.55 ± 30.6	0.29

[a] Values are given as mean ± standard deviation. (ms: milliseconds).

Statistically significant differences were found between the groups regarding the QT, QTc, Tp-e, Tp-e/QT ratio, Tp-e/QTc ratio, QTd, QTcd, Pd, JT, JTc, Tp-e/JT ratio and Tp-e/JTc ratio in the ECG measurements (Figs. 1, 2). The data are given in Table 2.

Comparison of QTc according to gender in case group, the mean QTc was 446.83 ± 13.0 for females and 438.44 ± 11.2 for males. The difference was statistically significant ($p = 0.012$).

Discussion

Breath holding spells are benign and common clinical conditions. In different studies, the prevalence has been reported as 4% to 27% of children between six months and six years old [22]. In a study by Olsen et al. [23], 30.6% of the children who had breath holding spells in childhood suffered from syncope attacks and 29.4% of these children had concentration problems in long term.

Iron deficiency is common in patients with breath holding spells and is considered to play a role in the pathogenesis but the mechanism is not clear. Iron is considered to play a role in catecholamine metabolism and neurotransmitter function. Decreased oxygen-carrying capacity due to iron deficiency anemia and decreased cerebral oxygenation is another suggested mechanism [24,25]. Even though iron deficiency anemia is common in children with breath holding spells, autonomic dysfunction is considered to be the main pathogenesis of this clinical entity.

As the heart rate increases (RR interval shortens), the QT interval shortens in the normal heart. Therefore, the corrected QT interval (QTc) adjusts the QT interval correctly for heart rate extremes using the preceding RR-interval [26]. QTd, QTcd and Tp-e interval, which are used to indicate ventricular conduction and the deterioration of myocardial oxygenation as a result of autonomic dysfunction, are considered as markers that reflect abnormal ventricular repolarization associated with arrhythmogenesis [13–17]. Akalin et al. [9] showed that QTd was increased from 44.8 ms to 59.5 ms and QTcd increased from 79.6 ms to 102.1 ms in 43 patients who had breath holding spells compared to 25 controls. Amoozgar et al. [21] showed that the QTcd was statistically different in the case and the control groups, 148.2 and 132 ms, respectively, but no significant change was found in QTd. Movahedian et al. [27] found that the QTd was 61.6 and 47.1 ms, and the QTcd was 104 and 71.9 ms, respectively in the case and the control groups. In our study, QTd was increased from 19.86 ms to 38.57 ms and QTcd was increased from 28.34 ms to 58.03 ms respectively in the case and the control groups, respectively, and the differences were statistically significant ($p < 0.001$).

Küçük et al. [28] found that the heart rate, Tp-e interval, Tp-e dispersion, Tp-e/QT and Tp-e/QTc ratios were statistically higher in patients with Down syndrome without congenital heart disease compared to the control group. Akın et al. [29] found that in children with subclinical hypothyroidism, minimal QT was lower than healthy children, meanwhile maximal QT, QTd, QTcd, Tp-e, Tp-e/QT ratio, and Tp-e/QTc ratio were higher. In this study we also investigated and compared the new indicators of ventricular repolarization in children with breath holding spells and the control group. In the control and the case groups, the mean Tp-e was 47.27 ms and 80.09 ms, the Tp-e/QT ratio was 0.16 and 0.26, the Tp-e/QTc ratio was 0.11 and 0.17, JT interval was 204.09 and 224.52 ms, JTc was 290.00 and 333.72 ms, Tp-e/JT was 0.23 and

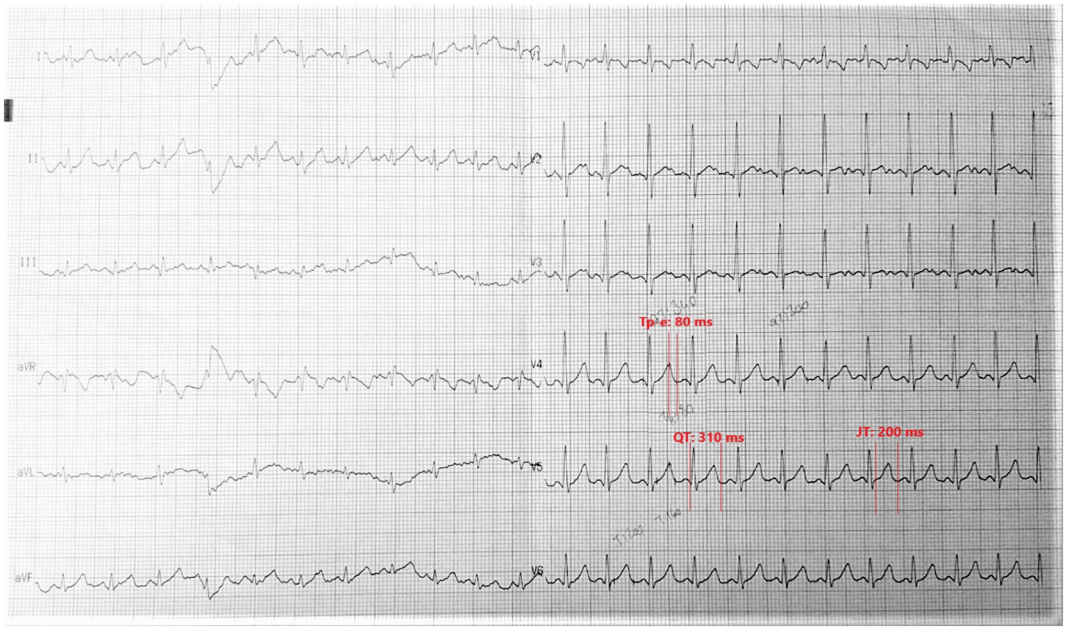

Fig. 1. ECG sample of a patient in case group.

0.35, Tp-e/JTc was 0.16 and 0.24, respectively and the differences between the groups were statistically significant ($p < 0.001$).

P-wave dispersion is a non-invasive method used to evaluate the risk of atrial fibrillation resulting from disruption of homogeneity and continuity in atrial conductivity. Autonomic dysfunction affects intra- and interatrial conduction resulting in inhomogeneity and discontinuity in atrial conduction system [21]. Imamoglu et al. [30] reported that Pd was increased in children with type 1 diabetes. In addition, Şimsek et al. [31] reported that the Pd was prolonged in adult patients with iron deficiency anemia due to autonomic dysfunction and tissue hypoxia. However, Amoozgar et al. [21] did not find a statistically significant difference in Pd in children with breath holding spells. In our study, the mean Pd was 29.32 ms in the control group and 40.53 ms in the case group and the difference was statistically significant ($p < 0.001$).

In our study, the mean heart rate was 125 bpm in the control group and 138 bpm in the case group, and the difference was significant ($p < 0.015$). This difference in heart rate may be resulting due to autonomic dysregulation in children with breath holding spells. Although we found differences in QT, QTc, Tp-e, Tp-e/QT ratio, Tp-e/QTc ratio, QTd, QTcd, Pd, JT, JTc, Tp-e/JT ratio and Tp-e/JTc ratio, there was no significant difference in terms of P, PR, QRS and T intervals, suggesting that these new indices are more valuable in indicating atrial conduction and ventricular repolarization.

The main limitation of our study was the lack of long-term follow-up of the patients. More evident ECG pathologies may be observed in the follow-up. Further investigation is needed for these new indices of ventricular repolarization in children with breath holding spells.

Conclusion

Ventricular repolarization and atrial conduction are affected in patients with breath holding spells. QT, QTc, Tp-e, Tp-e/QT ratio, Tp-e/

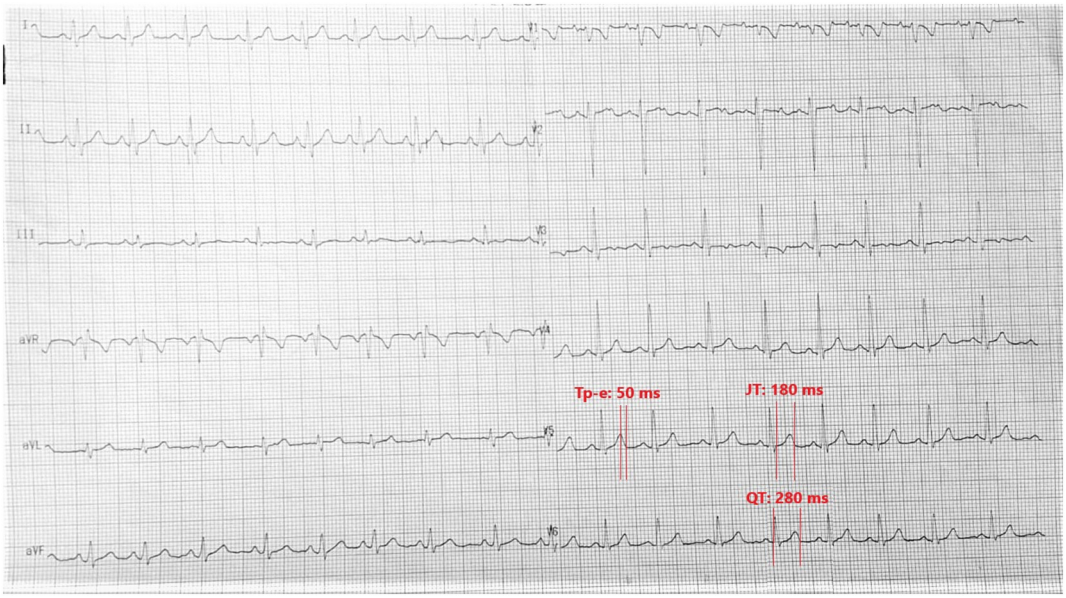

Fig. 2. ECG sample of a patient in control group.

Table 2
QT, QTc, Tp-e, Tp-e/QT ratio, Tp-e/QTc ratio, QTd, QTcd, Pd, JT, JTc, Tp-e/JT ratio, Tp-e/JTc ratio values in the case and the control groups.[a]

	Case	Control	p value
QT interval (ms)	296.64 ± 16.4	287.86 ± 27.0	0.045
QTc interval (ms)	442.93 ± 12.8	410.05 ± 21.3	<0.001
Tp-e (ms)	80.09 ± 15.3	47.27 ± 7.8	<0.001
Tp-e/QT ratio	0.26 ± 0.04	0.16 ± 0.02	<0.001
Tp-e/QTc ratio	0.17 ± 0.03	0.11 ± 0.01	<0.001
QTd (ms)	38.57 ± 11.4	19.86 ± 7.2	<0.001
QTcd (ms)	58.03 ± 17.8	28.34 ± 11.4	<0.001
Pd (ms)	40.53 ± 10.3	29.32 ± 15.6	<0.001
JT (ms)	224.52 ± 26.6	204.09 ± 22.7	<0.001
JTc (ms)	333.72 ± 26.2	290.00 ± 22.1	<0.001
Tp-e/JT ratio	0.35 ± 0.06	0.23 ± 0.04	<0.001
Tp-e/JTc ratio	0.24 ± 0.05	0.16 ± 0.03	<0.001

[a] Values are given as mean ± standard deviation. (ms: milliseconds).

QTc ratio, QTd, QTcd, Pd, JT, JTc, Tp-e/JT ratio and Tp-e/JTc ratio were significantly increased compared to healthy children. These increases may be considered as a sign of cardiac arrhythmia risk in breath-holding spells.

References

[1] Dalton R, Boris NW. Disruptive behavioral disorders. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, Zitelli BJ, Davis HW, editors. Nelson Textbook of Pediatrics. 18th ed. Philadelphia: Saunders Elsevier; 2007. p. 1226–9.
[2] DiMario Jr FJ, Burleson JA. Autonomic nervous system function in severe breath-holding spells. Pediatr Neurol 1993;9(4):268–74.
[3] FJ Jr DiMario. Breath-holding spells in childhood. Am J Dis Child 1992;146(1):125–31.
[4] Breningstall GN. Breath-holding spells. Pediatr Neurol 1996;14(2):91–7.
[5] Akalin F, Tirtir A, Yilmaz Y. Increased QT dispersion in epileptic children. Acta Paediatr 2003;92(8):916–20.
[6] DiMario Jr FJ, Bauer L, Baxter D. Respiratory sinus arrhythmia in children with severe cyanotic and pallid breath-holding spells. J Child Neurol 1998;13(9):440–2 Sep.
[7] Elming H, Holm E, Jun L, Torp-Pedersen C, Køber L, Kircshoff M, et al. The prognostic value of the qt interval and qt ınterval dispersion in a population of danish citizens. Euro Heart J 1998;19:1391–400.
[8] Day CP, McComp LM, Campbell RWF. QT dispersion: an indication of arrhythmia risk in patients with long QT Intervals. Br Heart J 1990;63(6):342–4 Jun.
[9] Akalin F, Turan S, Guran T, Ayabakan C, Yilmaz Y. Increased QT dispersion in breath-holding spells. Acta Paediatr 2004;93(6):728–30.
[10] Kolkiran A, Tutar E, Atalay S, Deda G, Cin S. Autonomic nervous system functions in children with breath-holding spells and effects of iron deficiency. Acta Paediatr 2005;94(9):1227–31.
[11] Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, et al. Prevalence of the congenital long-QT syndrome. Circulation 2009;120:1761–7.
[12] Pye M, Quinn AC, Cobbe SM. QT interval dispersion: a noninvasive marker of susceptibility to arrhythmia in patients with sustained ventricular arrhythmias? Br Heart J 1994;71:511–4.
[13] Kors JA, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. J Electrocardiol 2008;41:575–80.
[14] Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol 2008;41:567–74.
[15] Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. J Am Coll Cardiol 2000;36:1749–66.
[16] Wang JF, Shan QJ, Yang B, Chen ML, Zou JG, Chen C, et al. Tpeak-Tend interval and risk of cardiac events in patients with Brugada syndrome. Zhonghua Xinxueguanbing Zazhi 2007;35:629–32.
[17] Castro-Torres Y. Tpeak-Tend/QT: un nuevo predictor electrocardiográfico de muerte súbita cardíaca. Cardiocore 2014;49:86–7.
[18] Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation 1998;98:1928–36.
[19] Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, Dorantes Sánchez M, Dorticós Balea F, Zayas Molina R, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol 2006;47:1828–34.
[20] Berul CI, Sweeten TL, Dubin AM, Shah MJ, Vetter VL. Use of the rate-corrected JT interval for prediction of repolarization abnormalities in children. Am J Cardiol 1994;74(12):1254–7 Dec 15.
[21] Amoozgar H, Saleh F, Farhani N, Rafie M, Inaloo S, Asadipooya A. Cardiac repolarization changes in the children with breath-holding spells. Iran J Pediatr Dec 2013;23(6):687–92.
[22] Lombroso CT, Lerman P. Breath holding spells (cyanotic and pallid infantile syncope). Pediatrics 1967;39(4):563–81.
[23] Olsen AL, Mathiasen R, Rasmussen NH, Knudsen FU. Long-term prognosis for children with breath-holding spells. Dan Med Bull 2010;57(11):A4217.
[24] Daoud AS, Batieha A, Al-Sheyyab M, Abuekteish F, Hijazi S. Effectiveness of iron therapy on breath holding spells. J Pediatr 1997;130:547–50.
[25] Mocan H, Yıldıran A, Orhan F, Erduran E. Breath holding spells in 91 children and response to treatment with iron. Arch Dis Child 1999;81:261–2.
[26] Funck-Brentano C, Jaillon P. Rate-corrected QT interval: techniques and limitations. Am J Cardiol 1993 Aug 26;72(6):17B–22B.
[27] Movahedian AH, Heidarzadeh Arani M, Motaharizad M, Mousavi GA, Mosayebi Z. Evaluation of QT dispersion in children with breath holding spells. Iran J Child Neurol 2016;10(1):25–30.
[28] Küçük M, Karadeniz C, Ozdemir R, Meşe T. Prolonged T-wave peak-end interval in Down syndrome patients with congenitally normal hearts. Pediatr Int 2018;60(6):513–6 Jun.
[29] Akın A, Unal E, Yıldırım R, Türe M, Balık H, Haspolat YK. Evaluation of QT Dispersion and Tp-e interval in children with subclinical hypothyroidism. Pacing Clin Electrophysiol 2018;41(4):372–5 Apr.
[30] Imamoglu EY, Oztunc F, Eroglu AG, Onal H, Guzeltas A. Dispersion of the P wave as a test for cardiac autonomic function in diabetic children. Cardiol Young 2008;18(6):581–5.
[31] Simsek H, Gunes Y, Demir C, Sahin M, Gumrukcuoglu HA, Tuncer M. The effects of iron deficiency anemia on p wave duration and dispersion. Clinics (Sao Paulo) 2010;65(11):1067–71.