Asian Journal of Medicine and Health

5(2): 1-7, 2017; Article no.AJMAH.34397

The Association of Pseudoexfoliation Syndrome with Ventricular Repolarization Dynamics

Ayşe Kevser Demir[1], Selim Demir[2*], Arif Arısoy[3], Sait Alim[2], Alper Güneş[2], Rabia Pişkin Sağır[1], Fatih Altunkaş[3], Kayihan Karaman[3] and Şafak Şahin[1]

[1]Department of Internal Medicine, Faculty of Medicine, Gaziosmanpasa University, Tokat, Turkey.
[2]Department of Ophthalmology, Faculty of Medicine, Gaziosmanpasa University, Tokat, Turkey.
[3]Department of Cardiology, Faculty of Medicine, Gaziosmanpasa University, Tokat, Turkey.

Authors' contributions

This work was carried out in collaboration between all authors. Author AKD designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SD, AA, SA, AG, RPS, FA and KK managed the analyses of the study. Author SS managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJMAH/2017/34397
Editor(s):
(1) Ricardo Bonfim Silva, Faculdade de Medicina de Ribeirao Preto, Universidade de Sao Paulo, Brazil.
Reviewers:
(1) Emmanouil Magiorkinis, University of Athens Medical School, Greece.
(2) Ricardo Evangelista Marrocos de Aragao, Universidade Federal do Ceara Medicine, Brazil.
Complete Peer review History: http://www.sciencedomain.org/review-history/19696

Original Research Article

Received 26th May 2017
Accepted 16th June 2017
Published 25th June 2017

ABSTRACT

Pseudoexfoliation syndrome (PEX), an extracellular matrix disorder, is associated with an increased risk of heart diseases, including coronary arterial disease, myocardial ischemia, and arrhythmia. Ventricular repolarization abnormalities can be an indicator of these diseases. The primary objective of this study was to evaluate ventricular repolarization in patients with PEX by using noninvasive parameters. This prospective case-control study consisted of 32 patients with PEX and 32 controls without PEX. The diagnosis of PEX was made during a slit lamp ophthalmic examination upon the finding of white amyloid-like exfoliation material on the anterior capsule of the crystalline lens or iris. The QT dispersion (QTd), Tp-e interval, and Tp-e/QT ratio were measured from a 12-lead electrocardiogram. The Student's t-test and Chi-square test were used for statistical analysis. QTd was significantly increased in patients with PEX compared to the controls (42±17 vs. 25±15 ms, $P < 0.001$, respectively). The Tp-e/QT ratio was also significantly higher in patients with

**Corresponding author: E-mail: dr.selimdemir@yahoo.com;*

PEX (0.22±0.03 vs. 0.20±0.02, *P* = .021). There was no significant difference between the groups with respect to the Tp-e interval (90±13 ms vs. 85±10 ms, *P* = .119). Our study revealed that QTd and the Tp-e/QT ratio were increased in patients with pseudoexfoliation syndrome.

Keywords: Pseudoexfoliation syndrome; ventricular repolarization; QT dispersion; Tp-e interval; Tp-e/QT ratio.

1. INTRODUCTION

Pseudoexfoliation syndrome (PEX) is an extracellular matrix disorder characterized by age-induced accumulation of fibrillar material in many ocular tissues. The disease affects both genders equally and its frequency increases with age. Its frequency varies in different ethnic populations and geographic locations [1-3].

The syndrome is a systemic disease with specific ocular signs; however, the accumulation of amyloid-like fibrillar deposits are not only found within the anterior segment of the eye but also in various other locations in the body, including skin, lungs, liver, heart, cerebral meninges, and vessel walls [4,5]. Recent studies have revealed that PEX is associated with increased risk of cardiovascular diseases including angina [6], myocardial ischemia [7], coronary artery disease [8,9], and arrhythmia [10].

It has been proposed that interlead variability of the QT interval (QT dispersion, QTd) detected in standard electrocardiography (ECG) may be used as a marker of electrical instability of the heart [11]. QTd and the Tp-e interval have been suggested as noninvasive estimates for global ventricular myocardial repolarization [12,13]. It has also been documented that ECG parameters reflecting ventricular repolarization are associated with significant cardiovascular risk factors [14]. In this study, we evaluated ventricular repolarization in patients with PEX using the ECG findings of QTd, Tp-e interval, and Tp-e/QT ratio.

2. MATERIALS AND METHODS

2.1 Study Design

The present study was prospective, cross-sectional, and observational. The study was carried out in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of the Faculty of Medicine of Gaziosmanpaşa University (number: KAEK 2013/20). All patients were informed of the study protocol and written permission was obtained from each subject.

2.2 Study Population

Sixty-four patients, aged 60–80 years, who presented to the ophthalmology clinic at Gaziosmanpaşa University Hospital were enrolled in this study. The diagnosis of PEX was made at the clinic. The study group consisted of 32 patients (22 males; mean age 71.2±5.9 years) with PEX and the control group consisted of 32 patients (18 males; mean age 69.4±4.7 years) without PEX. Each participant underwent a detailed physical examination, cardiac auscultation, and electrocardiography in the internal medicine clinic at the hospital. Patients suspected of having cardiac disease underwent echocardiography at the hospital's cardiology clinic to exclude it.

Inclusion criteria for the study group were: (1) presence of PEX on slit-lamb biomicroscopy and (2) age interval of 60–80 years. The control group was composed of individuals with no evidence of PEX. Exclusion criteria of this study were valvular heart disease, previous cardiac surgery, coronary artery disease, bundle branch block, atrial fibrillation, paced rhythm, uncontrolled hypertension, hypertrophic or dilated cardiomyopathies, congenital heart disease, hypo- or hyper-thyroidism, malignancy, tachycardia (heart rate >100 beat/min), and pulmonary, hepatic, or renal dysfunction. Patients whose ECGs showed U waves or low-amplitude T waves (<0.1 mV) or whose QT interval was unable to be measured were also excluded.

2.3 Eye Examination and Diagnosis of Pseudoexfoliation Syndrome

A detailed ophthalmic examination including best-corrected visual acuity, measurement of intraocular pressure by applanation tonometry, slit-lamp biomicroscopy of the anterior chamber, and indirect fundus examination of the eye after cycloplegic pupil dilation was performed in all subjects. The diagnosis of PEX was based on

slit-lamp biomicroscopy that detected the presence of the typical whitish-gray deposits on the trabecular meshwork, corneal endothelium, iris, epithelium of the ciliary body, or anterior capsule of the lens.

2.4 Electrocardiography

Twelve-lead ECGs (Cardiofax V; Nihon Kohden Corp., Tokyo, Japan) with 10 mm/mV amplitude and 25 mm/sec rate were obtained from all patients, who were breathing freely in the supine position. A ×400% magnification was made using Adobe Photoshop software to decrease measurement errors after scanning. Two cardiologists who were blinded to the status of each subject made measurements on the computer. The average value of three measurements was calculated for each lead, after which the value obtained by each cardiologist was averaged together. If the measured ECG points were not clear, the patients were excluded. Intra observer and inter observer variation coefficients were 3.7% and 4.2%, respectively.

The RR interval (heart rate), QRS duration, QT interval, QTd, Tp-e interval, and Tp-e/QT ratio were measured in all derivations. The assessment of the ECG was performed according to the procedure described above [14]. Briefly, the QT interval was measured from the beginning of the QRS to the end of the isoelectric line of the T wave. Bazett's Formula was used to calculate the corrected QT interval (QTc). QTd was defined as the difference between the minimum and maximum QT interval of the 12 leads [15]. Similarly, the QTc dispersion (QTcd) was defined as the difference between the minimum and maximum QTc within the 12 leads. The average value of the three RR intervals was used for calculation of heart rate. The Tp-e interval was measured from lead V2 as the distance from the peak of the T wave to the end of the T wave, where the wave reached the isoelectric line [16].

2.5 Statistical Analyses

SPSS for Windows, version 18.0 (SPSS Inc., Chicago, USA) was used for all statistical analyses. Normality tests were performed on all measured variables. Continuous values are expressed as mean ± standard deviation (SD). Categorical data are expressed as numbers with percentages. The Student's t-test was used for normally distributed variables and the Chi-square test for categorical data. A *P*-value of <.05 was considered statistically significant. The PASS statistical program was used for power analysis, in order to determine statistically significant variables. It was shown that study powers of all statistically significant variables in this study were within a reliable range of 0.75–0.99.

3. RESULTS

The mean ages were 71.2±5.9 for the PEX group and 69.4±4.7 years for the control group. The male/female ratio was 22/10 in the PEX group and 18/14 in the control group (*P* > .05 for age and gender). There was no significant difference between the groups regarding diabetes mellitus (DM), hypertension (HT), or patients' smoking status. The baseline characteristics of the patients with PEX and controls are listed in Table 1.

Mean heart rate was 75±10 in the PEX group and 74±13 in the control group (*P* = .603). QTd, QTcd, Tp-e/QT ratio, and Tp-e/QTc ratio in the PEX patients were significantly higher than found in the controls (*P* <.001, *P*= .001, *P*=.021, and *P*=.024, respectively). Typical ECG records from a patient with PEX syndrome in comparison with normal ECG is presented in Fig. 1. There was no significant difference between the groups for the parameters of QT, QTc, Tp-e, and Tp-ec (*P* <.502, *P*= .222, *P*=.119, and *P*=.199, respectively). The detailed presentations of ECG parameters for both groups are listed in Table 2.

Table 1. Demographic variables of the study subjects

Variables	PEX (-) (n=32)	PEX (+) (n=32)	*P*
Age, year (min-max)	69.4±4.7 (60-78)	71.2±5.9 (60-80)	.180
Male gender, n (%)	18 (56)	22 (69)	.306
DM, n (%)	7 (22)	9 (28)	.567
HT, n (%)	16 (50)	18 (56)	.619
Smoking, n (%)	9 (28)	6 (19)	.380

DM: Diabetes mellitus; HT: Hypertension; PEX: Pseudoexfoliation syndrome

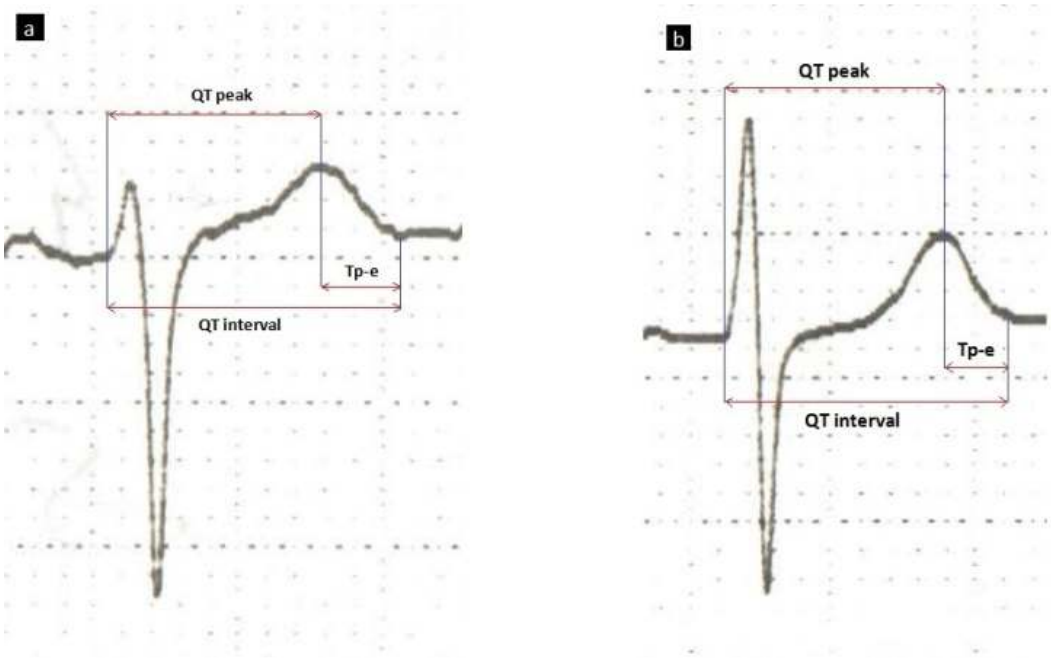

Fig. 1. Typical ECG records from a patient with PEX syndrome (a) in comparison with normal ECG (b)

Table 2. Comparison of electrocardiographic findings between the groups

Variables	PEX (-)	PEX (+)	*P*	Power
HR, beat/min	74±13	75±10	.603	-
*QT, ms (min-max)	379±28 (333-453)	373±35 (297-451)	.502	-
*QTc, ms (min-max)	423±36 (360-494)	412±35 (348-554)	.222	-
QTd, ms	25±15	42±17	**<.001**	**.99**
QTdc, ms	29±16	47±18	**.001**	**.99**
Tp-e, ms	85±10	90±13	.119	-
Tpe-ec, ms	95±14	99±16	.199	-
Tp-e/QT	0.20±0.02	0.22±0.03	**.021**	**.87**
Tp-e/QTc	0.20±0.03	0.22±0.03	**.024**	**.75**

HR: Heart rate; PEX: Pseudoexfoliation syndrome; QTc: corrected QT; QTd: QT dispersion; QTdc: corrected QT dispersion; Tp-e: T wave peak-to-end interval; Tp-ec: corrected Tp-e.

The data are presented as mean ± standard deviation. Student's t-test was used for comparison and statistically significant P values were presented in bold.

** Lead V2 was used for measuring the QT value*

4. DISCUSSION

Extraocular circumstances such as Alzheimer's-type dementia [17], sensor ineural [18], and cardiovascular disease [8,9] are likely to be observed in patients with PEX syndrome. There is a growing body of clinical and laboratory evidence that indicates many cardiovascular implications are associated with PEX [19]. It has been recently linked to several cardiovascular disorders, including abdominal aortic aneurysm [20], renal artery stenosis [21], subclinical myocardial infarction [7], coronary artery disease [9], angina [6], arrhythmia [10], and hypertension [6].

Recent studies have also shown that PEX material is widely distributed throughout the body, including the blood vessels [4,5]. The endothelium plays a key role in regulating vascular function by secreting a variety of constricting and dilating substances. In their study, Atalar et al. [22] evaluated brachial artery endothelial function by vascular response to reactive hyperemia (flow-mediated dilation and sublingual nitroglycerin-mediated dilation) using

high-resolution ultrasound and found that patients with PEX had significantly lower flow-mediated dilation. Their findings indicate that systemic endothelial function is impaired in patients with PEX. Another study found an association between PEX and a recently discovered proinflammatory protein, YKL-40 [23]. It is suggested that the protein plays a role in the pathogenesis of endothelial dysfunction [24] and coronary artery diseases [25].

There is a link between endothelial dysfunction of coronary or peripheral arteries and chronic heart failure [26]. Cardiac function and hemodynamics are easily detectable by echocardiography. Yılmaz et al. [27] evaluated left ventricular functions in patients with PEX by using tissue Doppler imaging. They documented decreased left ventricular diastolic functions correlated with plasma B-type natriuretic peptide levels in PEX patients. In another study using tissue Doppler imaging, Demir et al. [7] found that there may also be an association between PEX and subclinical myocardial ischemia, even when patients exhibit no signs or symptoms of ischemia. Similarly, Bojic et al. [28] emphasized the possibility of an association between patients with PEX and a discrete asymptomatic myocardial diastolic dysfunction.

The QTd, Tp-e interval, and Tp-e/QT ratio are accepted as markers of dispersion of ventricular repolarization [14]. QT dispersion is used as an index of the spatial dispersion of ventricular recovery times. Increased QTd and QTdc durations are generally linked to dispersion of ventricular repolarization and it has been documented that these parameters are significant findings of patients who are at risk for sudden death [29]. In a recent study, it was found that QTd, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc were significantly increased in patients with coronary slow flow, which is associated with endothelial dysfunction, decreased nitric oxide level, and microvascular abnormalities [14]. In the present study, we found that the QTd and QTdc intervals were significantly increased in patients with PEX compared with controls.

The measurement of Tp-e is a debated issue. However, it was suggested that Tp-e measurements should be limited to precordial leads, because these leads more accurately reverberate transmural dispersion of repolarization [16]. Researchers have used lead V2 [14], V5 [30], or V6 [31] to measure the Tp-e interval. Wolk et al. [32] designed a study to investigate changes in the Tp-e interval and other well-known indices of electrical dispersion in patients with hypertensive left ventricular hypertrophy. They measured the Tp-e interval in all leads from a 12-lead ECG and found that only lead V2 provided a measurement that was significantly different in patients with hypertensive left ventricular hypertrophy. Therefore, in this study, we used only lead V2 for Tp-e measurement.

The ECG manifestation of ventricular repolarization is the T wave. The Tp-e interval can be used as an index of global dispersion of ventricular repolarization. Sicouri and Antzelevich showed an association between Tp-e interval prolongation and arrhythmias [33]. The Tp-e interval prolongation is linked with cardiovascular diseases. Higher Tp-e/QT and Tp-e/QTc ratios were found in patients with obstructive sleep apnea [34] and coronary slow flow [14]. In this study, we found that the Tp-e/QT ratio is higher in patients with PEX. Although the Tp-e interval was prolonged in patients with PEX in this study, the difference was not statistically significant. The presence of coronary endothelial dysfunction in patients with PEX may cause ventricular repolarization irregularities and, in turn, produce cardiac findings on an ECG.

Our study has several limitations. There were a relatively small number of individuals included in the study. We did not evaluate the association between ventricular arrhythmias and the evaluated ECG parameters. Therefore, a definitive conclusion on the prognostic importance of Tp-e interval prolongation and higher Tp-e/QT ratio in our patients cannot be made. Because patients with cardiac diseases were excluded, this study is somewhat limited, comparing only patients with PEX who had no cardiac disease (except HT) and controls. We performed echocardiography only in patients in whom, after physical examination, auscultation, and electrocardiography, cardiac disease was suspected. The results would be more widely applicable if all patients underwent echocardiography. Both groups included individuals with DM or HT; it would be better if the study excluded such patients. Due to these limitations, this study can make no definitive conclusion regarding cardiac diseases in patients with PEX. Finally, the prognostic role of QTd, Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios in patients with PEX needs to be investigated.

5. CONCLUSION

This study is the first study to report the relationship among QTd, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio with the PEX. Significantly, we found that mean QTd, Tp-e/QT ratio, and Tp-e/QTc ratio are increased in patients with PEX. Our findings indicate increased ventricular repolarization heterogeneity in patients with PEX, which may elucidate the increased prevalence of cardiovascular diseases in patients with the syndrome.

CONSENT

Informed consent was obtained from patients who participated in this study.

ETHICAL APPROVAL

Ethics committee approval was received for this study from local ethics committee.

DISCLAIMER

Some part of this manuscript was previously presented in the following conference.
Conference name: 17th National Internal Medicine Congress of Turkey.
Dates: October 14-18, 2015
Location: Antalya, Turkey.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Forsius H. Prevalence of pseudoexfoliation of the lens in Finns, Lapps, Icelanders, Eskimos, and Russians. Trans Ophthalmol Soc UK. 1979;99(2):296-8.
2. McCarty CA, Taylor HR. Pseudoexfoliation syndrome in Australian adults. Am J Ophthalmol. 2000;129(5):629-33.
3. Young AL, Tang WW, Lam DS. The prevalence of pseudoexfoliation syndrome in Chinese people. Br J Ophthalmol. 2004; 88(2):193-5.
4. Hollo G. Exfoliation syndrome and systemic cardiovascular diseases. J Glaucoma. 2014;23(8 Suppl 1):9-11.
5. Schlotzer-Schrehardt UM, Koca MR, Naumann GO, Volkholz H. Pseudoexfoliation syndrome. Ocular manifestation of a systemic disorder? Arch Ophthalmol. 1992;110(12):1752-6.
6. Mitchell P, Wang JJ, Smith W. Association of pseudoexfoliation syndrome with increased vascular risk. Am J Ophthalmol 1997;124(5):685-7.
7. Demir N, Ulus T, Yucel OE, Kumral ET, Singar E, Tanboga HI. Assessment of myocardial ischaemia using tissue Doppler imaging in pseudoexfoliation syndrome. Eye (Lond). 2011;25(9):1177-80.
8. Andrikopoulos GK, Mela EK, Georgakopoulos CD, et al. Pseudoexfoliation syndrome prevalence in Greek patients with cataract and its association to glaucoma and coronary artery disease. Eye (Lond). 2009;23(2): 442-7.
9. Citirik M, Acaroglu G, Batman C, Yildiran L, Zilelioglu O. A possible link between the pseudoexfoliation syndrome and coronary artery disease. Eye (Lond). 2007;21(1): 11-5.
10. Brajkovic J, Surac IK, Ercegovic A, Miletic-Juric A, Susic N, Buric Z. Ocular Pseudoexfoliation syndrome and internal systemic diseases. Acta Clin Croat. 2007; 46(suppl 1):57-61.
11. Day CP, McComb JM, Campbell RW. QT dispersion: An indication of arrhythmia risk in patients with long QT intervals. Br Heart J. 1990;63(6):342-4.
12. Dilaveris P, Gialafos E, Poloniecki J, et al. Changes of the T-wave amplitude and angle: An early marker of altered ventricular repolarization in hypertension. Clin Cardiol. 2000;23(8):600-66.
13. Xia Y, Liang Y, Kongstad O, Holm M, Olsson B, Yuan S. Tpeak-Tend interval as an index of global dispersion of ventricular repolarization: Evaluations using monophasic action potential mapping of the epi- and endocardium in swine. J Interv Card Electrophysiol. 2005;14(2):79-87.
14. Karaman K, Altunkas F, Cetin M, et al. New markers for ventricular repolarization in coronary slow flow: Tp-e Interval, Tp-e/QT Ratio, and Tp-e/QTc Ratio. Ann Noninvasive Electrocardiol. 2015;20(4): 338-44.
15. Bazett H. An analysis of the time relations of electrocardiograms. Heart. 1920;7:353-67.
16. Antzelevitch C. T peak-Tend interval as an index of transmural dispersion of repolarization. Eur J Clin Invest. 2001; 31(7):555-7.

17. Cumurcu T, Dorak F, Cumurcu BE, Erbay LG, Ozsoy E. Is there any relation between pseudoexfoliation syndrome and Alzheimer's type dementia? Semin Ophthalmol. 2013;28(4):224-9.
18. Samarai V, Samarei R, Haghighi N, Jalili E. Sensory-neural hearing loss in pseudoexfoliation syndrome. Int J Ophthalmol. 2012;5(3):393-6.
19. Katsi V, Pavlidis AN, Kallistratos MS, et al. Cardiovascular repercussions of the pseudoexfoliation syndrome. N Am J Med Sci. 2013;5(8):454-9.
20. Djordjevic-Jocic J, Jovanovic P, Bozic M, Tasic A, Rancic Z. Prevalence and early detection of abdominal aortic aneurysm in pseudoexfoliation syndrome and pseudoexfoliation glaucoma. Curr Eye Res. 2012;37(7):617-23.
21. Gonen KA, Gonen T, Gumus B. Renal artery stenosis and abdominal aorta aneurysm in patients with pseudoexfoliation syndrome. Eye (Lond). 2013;27(6):735-41.
22. Atalar PT, Atalar E, Kilic H, et al. Impaired systemic endothelial function in patients with pseudoexfoliation syndrome. Int Heart J. 2006;47(1):77-84.
23. Turkyilmaz K, Oner V, Kirbas A, et al. Serum YKL-40 levels as a novel marker of inflammation and endothelial dysfunction in patients with pseudoexfoliation syndrome. Eye (Lond). 2013;27(7):854-9.
24. Malyszko J, Koc-Zorawska E. YKL-40, a marker of cardiovascular disease and endothelial dysfunction, in kidney transplant recipients. Transplant Proc. 2014;46(8):2651-3.
25. Kastrup J, Johansen JS, Winkel P, et al. High serum YKL-40 concentration is associated with cardiovascular and all-cause mortality in patients with stable coronary artery disease. Eur Heart J. 2009; 30(9):1066-72.
26. Fischer D, Rossa S, Landmesser U, et al. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death. Eur Heart J. 2005;26(1):65-9.
27. Cicek Yilmaz D, Yilmaz A, Goksel I, Cirit A, Sen F, Tamer L. Evaluation of left ventricular functions in patients with pseudoexfoliation syndrome using tissue Doppler echocardiography and its association with plasma BNP levels. Anadolu Kardiyol Derg. 2014;14(5):422-6.
28. Bojić L, Ermacora R, Polić S, et al. Pseudoexfoliation syndrome and asymptomatic myocardial dysfunction. Graefes Arch Clin Exp Ophthalmol. 2005; 243(5):446-9.
29. Molnar J, Somberg JC. QT dispersion: Still a useful measurement. Cardiology. 2009; 112(3):165-7.
30. Barbhaiya C, Po JR, Hanon S, Schweitzer P. Tpeak - Tend and Tpeak - Tend /QT ratio as markers of ventricular arrhythmia risk in cardiac resynchronization therapy patients. Pacing Clin Electrophysiol. 2013; 36(1):103-8.
31. Letsas KP, Weber R, Astheimer K, Kalusche D, Arentz T. Tpeak-Tend interval and Tpeak-Tend/QT ratio as markers of ventricular tachycardia inducibility in subjects with Brugada ECG phenotype. Europace. 2010;12(2):271-4.
32. Wolk R, Mazurek T, Lusawa T, Wasek W, Rezler J. Left ventricular hypertrophy increases transepicardial dispersion of repolarisation in hypertensive patients: a differential effect on QTpeak and QTend dispersion. European Journal of Clinical Investigation. 2001;31(7):563-9.
33. Sicouri S, Antzelevitch C. A subpopulation of cells with unique electrophysiological properties in the deep subepicardium of the canine ventricle. The M cell. Circ Res. 1991;68(6):1729-41.
34. Kilicaslan F, Tokatli A, Ozdag F, et al. Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio are prolonged in patients with moderate and severe obstructive sleep apnea. Pacing Clin Electrophysiol. 2012;35(8): 966-72.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/19696