Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.12.847 2020;27(3):874-8

Original Article

The effect of transcatheter aortic valve implantation on ventricular repolarization indices and neutrophil-to-lymphocyte ratio

Hakan Kaya

Adiyaman University, Faculty Of Medicine, Department of Cardiology, Adiyaman, Turkey

Abstract

Aim: The electrocardiographic QT dispersion (QTd), Tpe/QT ratio and Tpeak-Tend (Tpe) interval have been known as ventricular repolarization indices. Neutrophil–to- lymphocyte ratio (NLR) is an inflammatory marker that is newly described. Increased QTd, Tpe/QT ratio, inflammation and Tpe interval are associated with ventricular arrhythmia (VA). In patients with severe aortic stenosis (AS), VA has a key role in terms of morbidity and mortality. The present study aimed at examining whether transcatheter aortic valve implantation (TAVI) affects ventricular repolarization indices and NLR.

Material and Methods: Study population consisted of a total of 44 patients undergoing TAVI. Echocardiographic and laboratory parameters of patients were evaluated before TAVI and sixth month after TAVI. Comparioson of electrocardiographic QTd, Tpe/QT ratio, Tpe interval and NLR of the same petients were made before TAVI and sixth month after TAVI.

Results: QT interval, corrected QT interval and heart rate were similar before and after TAVI ($p>0.05$ for all). There was a statistically significant decrease in QTd (26.0±9.1 vs. 21.3±7.2 ms; $p=0.008$), Tpe interval (88.43±12.6vs. 78.8±10.1 ms; $p<0.001$), NLR (3.08±2.0 vs. 2.16±0.73; $p=0.001$) and Tpe/QT ratio (0.23±0.3 vs. 0.21±0.1; $p=0.024$) after TAVI. Morever, the reduction in the Tpe interval and Tpe / QT ratio after TAVI was found to be significantly correlated with NLR ($r=0.400$, $p=0.007$; $r=0.396$, $p=0.008$; respectively).

Conclusion: TAVI does not only reduce symptoms in patients with severe AS, but may also be effective in reducing risk of VA by improving factors affecting ventricular repolarization.

Keywords: Aortic stenosis; neutrophil-to-lymphocyte ratio; transcatheter aortic valve implantation;ventricular arrhythmia

INTRODUCTION

Calcific degeneration is the most common causes of AS. Angina, syncope and heart failure are the major presentations of this disease and symptomatic severe AS was shown to be related to high mortality of about 50% (1, 2). Increased chronic pressure in left ventricule causes hypertrophy in patients with AS which consequently may lead to sudden cardiac death and ventricular arrhythmia (VA) (3).The prediction of VA can be assess using different methods such as corrected QT dispersion (cQTd), QT dispersion (QTd), QT interval (QT) and corrected QT interval (QTc). Morever, Tpe/QT ratio and electrocardiographic Tpeak to Tend (Tpe) interval can be used for the prediction of VA (4,5).

White blood cell count (WBC), including neutrophil and lymphocyte counts, is defined as systemic inflammation indicators (6). As a novel inflammatory marker for prognosis of systemic inflammatory response Neutrophil-to-lymphocyte ratio (NLR) is recently propose. Enhanced inflammatory activity is asserted to be involved in the pathogenesis of arrhythmia (7,8). Association between NLR and the severity of AS has been issued in previous studies (9,10).

The gold standard treatments for AS is surgical aortic valve replacement. However, transcatheter aortic valve implantation (TAVI), for severe AS patients who are not deemed suitable for surgical aortic valve replacement due to high-risk, is become an alternative procedure (11). There are limited data investigating the effect of TAVI on ventricular repolarization indices and NLR in patients with AS.

Goal of present study is to examine, in patients with severe AS, the effect of TAVI on ventricular repolarization indices and NLR.

Received: 23.12.2019 **Accepted:** 03.02.2020 **Available online:** 13.03.2020
Corresponding Author: Hakan Kaya, Adiyaman University, Faculty Of Medicine, Department of Cardiology, Adiyaman, Turkey
E-mail: kardiyolog02@gmail.com

MATERIAL and METHODS

Study design and study population

All of consecutive patients (n: 63) were participated in the study, all of whom underwent TAVI by using Edwards SAPIEN heart valve due to symptomatic severe AS between January 2017 and November 2019. Obtained Informed consent from all patients. The study ethical approval has from the committee based on the Declaration of Helsinki. Demographic data of patients including gender, body mass index, hypertension, diabetes mellitus, age and smoking status were recorded. Patients with hematopoietic disease, infective endocarditis or clinical evidence of any active infection, current steroid or chemotherapy treatment, autoimmune or inflammatory diseases, cancer, acute coronary syndrome, permanent cardiac pacemaker, non-sinus rhythm in ECG, congenital long-QT syndrome, systemic rheumatoid disease, coronary artery disease, ventricular extra-systoles, atrioventricular conduction disturbance, abnormal serum electrolyte levels, taking medicines affecting ventricular repolarization indices and use of antiarrhythmic drugs were omitted from the study. Nineteen patients were left out from the study according to exclusion criteria (5 patients had paroxysmal atrial fibrillation, 10 patients had severe coronary artery disease, 3 patients used antiarrhythmic drugs and one patient died due to stroke). Final study population was composed of 44 patients (23 male with a mean age of 72.41±7.89 years) who underwent TAVI via transfemoral approach.

Study protocol

Assessment of the patients were made by a special, multidisciplinary heart team. Society of Thoracic Surgeons score> 10% or Logistic EuroSCORE> 20% were used for clinical decision. All patients underwent TAVI due to high surgical risk. Electrocardiographic, echocardiographic and laboratory parameters were recorded for all patients. QTd, Tpe interval, Tpe / QT ratio, echocardiographic parameters, NLR were recorded before TAVI and compared to sixth month follow up measurements of the same patients after TAVI.

Electrocardiography

The 12-lead ECG was used for each patient with sinus rhythm (25mm/s rate). The heart rate was obtained from ECG measurements. Values of QT interval and Tpe interval were calculated from surface ECG by double-blinded cardiologists in order to minimalize the errors. U waves from ECGs were one of the exclusion criteria. Described QT interval as the interval from the initial of the QRS complex to the end of the T wave. QT interval was assessed in all of 12 electrodes as much as possible. The distiction between the minimum and maximum QT interval is identified QTd. For QTc interval, QT intervals were corrected according to heart rates (12). Tpe interval was described as the interval from the peak of T wave to the end of T wave. Measurement of Tpe interval was performed using precordial leads. Tpe/QT ratio and cQTd were obtained from these measurements.

Echocardiography

Echocardiography findings including left ventricle ejection fraction, mean aortic valve gradient, ventricular posterior and septal wall thicknesses, maximum aortic valve gradient, aortic valve area were obtained with the help of standard transthoracic M-mode based on two dimensional echocardiographic studies. A mean aortic valve gradient of ≥ 40 mmHg or an aortic valve area (AVA) of ≤ 1 cm2 is defined severe AS (13).

TAVI procedure

All TAVI procedures were performed under local anesthesia and deep sedation via transfemoral approach. Under rapid ventricular pacing, balloon aortic valvuloplasty was performed for both balloon sizing and stenotic valve dilatation. Finally, the Edwards SAPIEN heart valve was implanted with rapid ventricular pacing after valve positioning with the guidance of fluoroscopy.

Laboratory parameters

Peripheral venous blood samplewas taken by using antecubital vein after a 12-hour fasting period..Coulter LH 780 Hematology Analyzer (Architect plus ci16200 Abbott Illinois, USA) was used in order to measure the hematological parameters including total white blood cell, neutrophil and lymphocyte counts. Blood samples were collected one hour before TAVI and sixth month after the procedure. NLR was figured out by dividing the total neutrophil count to total lymphocyte count.

Statistical analysis

Data were analysed using SPSS (v 22.0, Chicago, IL, USA). Categorical and numerical variables were expressed as percentage and mean±SD, respectively. The normal distribution of values was evaluated with Kolmogorov-Smirnov test and histogram. Wilcoxon-rank test and paired-t test were used for continuous variables. For the correlation analysis Pearson or Spearman correlation coefficients were used, when suitable. Significance of P value was deemed under 0.05.

RESULTS

Demographic dataof patients are presented in Table 1. Electrocardiographic, echocardiographic and laboratory parameters before and after TAVI are presented in Table 2.

Table 1. Demographic characteristics of the study population

	Mean ± SD	n=44
Age (years)	72.4 ± 7.8	
STS Score	10.9 ± 1.9	
Logistic EuroSCORE	24.0 ± 4.2	
BMI, kg/m^2	25.1 ± 2.0	
Gender, male, n %		23 (52.3)
DM, n %		10 (22.7)
Hypertension, n %		29 (65.9)
Smoking, n %		16 (36.4)

BMI - body mass ındex, DM - diabetes mellitus, STS - Society of the Thoracic Surgeons.

Table 2. Electrocardiographic, echocardiographic, and laboratory parameters before and after TAVI

	Before TAVI (n=44)	After TAVI (n=44)	P value
Heart rate, beats/min	72.5 ± 11.2	70.8 ± 11.5	0.321
QT, ms	384.5 ± 44.3	376.1 ± 35.2	0.113
cQT, ms	417.9 ± 48.5	411.6 ± 36.4	0.132
QTd,ms	26.0 ± 9.1	21.3 ± 7.2	0.008
cQTd, ms	29.8 ± 10.8	24.2 ± 1.3	0.006
Tpe, ms	88.43 ± 12.6	78.8 ± 10.1	<0.001
Tpe/QT	0.23 ± 0.3	0.21 ± 0.1	0.024
LVEF %	51.3 ± 8.5	55.5 ± 5.8	<0.001
IVS, mm	14.1 ± 1.7	12.6 ± 1.1	0.003
PW, mm	13.4±0.8	11.8 ± 0.7	0.002
Mean gradient, mmHg	49.0 ± 8.5	8.1 ± 0.8	<0.001
WBC, 10^3/µl	8.9 ± 2.6	7.9 ± 2.1	0.069
Neutrophil count, 10^3/µl	5.4 ± 1.9	4.6 ± 1.4	0.008
Lymphocyte count, 10^3/µl	2.0 ± 0.8	2.2 ± 0.7	0.026
Neutrophil/lymphocyte ratio	2.9 ± 2.0	2.1 ± 0.7	0.001

QT - QT interval, cQT - corrected QT interval, QTd - QT dispersion, cQTd - corrected QT dispersion, Tpe – Tpeak to Tend interval, LVEF - left ventricular ejection fraction IVS – interventricular septum, PW – posterior wall, WBC - white blood cell count

Aortic valve gradient decreased significantly after a successful TAVI procedure (49.0±8.5 vs. 8.1±0.8 mmHg; p<0.001). A statistically significant improvement in left ventricle ejection fraction, interventricular septum thickness and posterior wall thickness was found after TAVİ (51.3±8.5, 55.5±5.8, p<0.001; 14.1±1.7, 12.6±1.1 mm, p=0.003;13.4±0.8, 11.8 ± 0.7 mm, p=0.002; respectively).

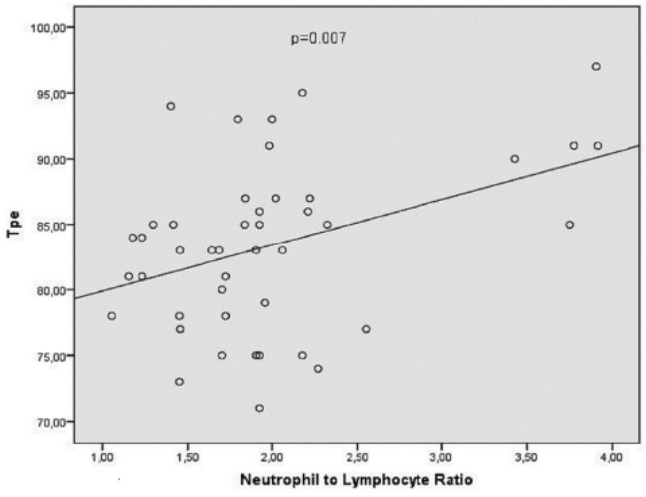

Figure 1. Correlation between the Tpe interval and neutrophil-to-lymphocyte ratio after TAVI

QT interval, QTc interval and heart rate were similar before and after TAVI (p>0.05 for all). QTd (26.0±9.1 vs. 21.3±7.2 ms; p=0.008), cQTd (29.8±10.8 vs. 24.2±1.3 ms; p=0.006), Tpe interval (88.43±12.6 vs.78.8±10.1 ms;

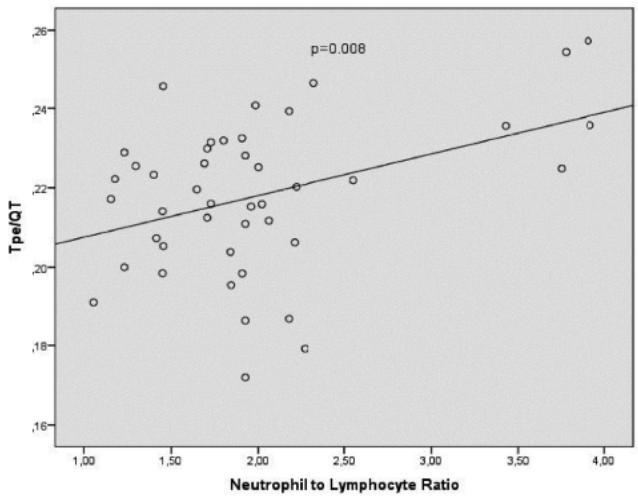

Figure 2. Correlation between the Tpe/QT ratio and neutrophil-to-lymphocyte ratio after TAVI

p<0.001), Tpe/QT ratio (0.23±0.3 vs.0.21±0.1; p=0.024) and NLR (3.08±2.0 vs. 2.16±0.73; p=0.001) were declined in a statistical significant manner sixth month after TAVI. The reduction in the Tpe interval after TAVI was found to be significantly correlated with NLR (r=0.400, p=0.007) (Figure 1).The reduction in the Tpe / QT ratio after TAVI was also found to be significantly correlated with NLR (r=0.396, p=0.008) (Figure 2).

DISCUSSION

This study evaluated the impact of TAVI on ventricular repolarization indices and NLR in subjects with severe

AS. It has been found that, QTd, cQTd, Tpe interval, Tpe/QT ratio and NLR have reduced sixth month after TAVI in patients with severe AS. In addition, the reduction in the Tpe interval and Tpe/QT ratio after TAVI was found to be significantly correlated with NLR

AS has still been one of the most common acquired valvular heart diseases and its prevalence is gradually increasing. After the onset of symptoms, the average life expectancy is approximately two years with heart failure, three years with syncope and five years with angina (14). Aortic valve replacement has still been considered as a gold standard approach tosubjects with severe symptomatic AS. However, some subjects are not suitable for surgery due to contraindications or co-morbidities. TAVI has become an alternative procedure for these patients (15,16). Malign VA is the main reason of sencope and sudden cardiac death in patients with symptomatic AS (17). Schwartz et al. studied patients with AS presenting syncope and detected malign ventricular arrhytmias during syncope (18). In a study by using 24-hour ambulatory rhythm holter recordings, Klein et al. found that complex VA frequency was greater in those with AS than the control group (19). QTd reflects the regional heterogenity of the ventricular repolarization patern (20). Prolonged QTd has been shown to be related to the risk of sudden cardiac death and ventricular tachyarrhythmias (21). Tpe interval was evaluated in several studies and found out to be a valuable index in predicting not only VA but also cardiovascular mortality. However, the variations of heart rate and body weight affect Tpe interval (22). As compared to QTd and cQTd, Tpe/QT ratio seems independent of variations in heart rate, and, as a consequence, recent studies proposed it as a more sensitive novel index for the dispersion of ventricular repolarization (22,23). Tokatlı et al. found that the Tpe interval and Tpe/QT ratio, were extended in those with diabetes mellitus (24). Zehir et al. Revealed that the Tpe interval increased in patient with coronary slow flow (25). Yayla et al. demonstrated that the Tpe interval and Tpe/QT ratio increased in subjects with severe AS (26). However, there is little data regarding the impact of TAVI on ventricular repolarization indices. Kahraman et al. demonstrated that the Tpe interval was shortened and Tpe/QT ratio was decreased in those with severe AS after TAVI (27). Contrary to this study, more objective results were obtained in mystudy as lused other ventricular repolarization indices like QTd and cQTd besides the Tpe interval and Tpe/QT ratio. Improvement of ventricular repolarization after TAVI can be explained by various mechanisms. Reduction of left ventricular wall thickness and stress may promote oxygen reserve and improve the ventricular repolarization. Microvascular dysfunction was shown in patients with normal coronary arteries but left ventricular hypertrophy (28). Another study demonstrated that severe AS patients with normal coronary arteries have microvascular perfusion defects (29). Microvascular dysfunction causes remodelling in ATP sensitive potassium channels in cellular base and may trigger myocardial electrical activities (30). Besides, left ventricular hypertrophy may induce myocardial fibrosis and effect the ventricular electrical conduction. In this study, a statistically significant improvement in left ventricle ejection fraction and left ventricle wall thickness was found. Unlike previous studies, the effect of TAVİ on the novel inflammatory marker NLR was also evaluated in this sudy. The role of inflammation in cardiovascular disorders has been well known. The NLR is a novel marker for inflammation and oxidative stress. Association of high NLR with poor clinical outcome in various cardiac diseases, including acut coronary syndrome and heart failure, was demonstrated in previous studies. (31,32). Furthermore, relationship between NLR and the severity of AS have also been discussed in previous studies (10,33). Aortic valve interstitial cells play an important role in providing valve homeostasis (34). Mechanical stress or hemodynamic causes such as bicuspid aorta damage these cells. Then, the inflammatory cells migrate to the damaged areas. Infiltration of inflammatory and immune cells and lipid retention stimulate valve interstitial cells. This activation can initiate the process of valve calcification and sclerosis. Neutrophils reflect the stage of subclinical inflammation which can cause the damage to endothelial cells and valve interstitial cells. The NLR value is the result of two important and opposite immune approaches. NLR is not affected by the acute inflammation unlike the absolute value of simple neutrophils. Enhanced inflammatory activity is assumed to be associated with arrhythmia (8). According to this study results NLR was found to be reduced in patients with severe AS after TAVİ and the reduction in the Tpe interval and Tpe/QT ratio after TAVI was found to be significantly correlated with NLR. Reduced inflammation after TAVİ in patients with severe AS may be another reason for decrease in ventricular repolarization indices. The major limitations of the study are small size of study population and lack of patients follow-up for ventricular arrhytmias.

CONCLUSION

As a result, I found statistically significant reduction in ventricular repolarization indices QTd, cQTd, Tpe interval and Tpe/ QT ratio after TAVI in subjects with severe AS. The results of this study revealed that NLR, a novel inflammatory marker, was significantly decreased after TAVI in patients with severe AS. Morever, the reduction in the Tpe interval and Tpe / QT ratio after TAVI was found to be significantly correlated with NLR. According to the present results, TAVI does not only reduce symptoms in patients with severe AS, but may also be effective in reducing risk of VA by improving factors affecting ventricular repolarization. Nevertheless, there is a need for multicentre studies with larger patient population and long-term follow up for ventricular arrhytmias in this population.

Financial Disclosure: There are no financial supports.

Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

Hakan Kaya ORCID: 0000-0002-5925-5150

REFERENCES

1. Carabello BA, Paulus WJ. Aortic stenosis. Lancet 2009; 373:956-66.
2. Kvidal P, Bergström R, Malm T. Long-term follow-up of morbidity and mortality after aortic valve replacement with a mechanical valve prosthesis. Eur Heart J 2000; 21:1099-111.
3. Levy D, Anderson KM, Plehn J, et al. Echocardiographicallydetermined left ventricular structural and functional correlatesof complex or frequent ventricular arrhythmias on one-hourambulatory electrocardiographic monitoring. Am J Cardiol 1987;59:836-40.
4. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F,et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricularfibrillation in patients with the Brugada syndrome. J Am Coll Cardiol 2006;47:1828-34.
5. Antzelevitch C, Sicouri S, Di Diego JM, et al. Does Tpeak-Tend provide an index of transmural dispersion of repolarization? Heart Rhythm 2007;4:1114-6.
6. Pereira IA, Borba EF. The role of inflammation, humoral and cell mediated autoimmunity in thepathogenesis of atherosclerosis. Swiss Med Wkly 2008;138:534-39.
7. L agrand WK, Visser CA, Hermens WT, et al. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation 1999;100:96-102.
8. Mountantonakis S, Deo R. Biomarkers in atrial fibrillation, ventricular arrhythmias and sudden cardiac death. Cardiovasc Ther 2012;30:74-80.
9. Avci A, Elnur A, Göksel A,et al. The relationship between neutrophil/lymphocyte ratio andcalcific aortic stenosis. Echocardiography 2014;31:1031-5.
10. Kucukseymen S, Cagirci G, Guven, R, et al. Is neutrophyl to lymphocyte ratio really auseful marker for all grades of degenerative aortic stenosis? Turk Kardiyol Dern Ars 2017;45:506-13.
11. Makkar RR, Fontane GP, Jilaihawi H,et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenonsis. N engl J Med 2012; 366:1696-704.
12. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal." J Cardiovasc Electrophysiol 2006;17:333-6.
13. Vahanian A, Alfieri O, Andreotti F,et al. Guidelines on themanagement of valvular heart disease: The Task Force on theManagement of Valvular Heart Disease of the European Societyof Cardiology. Eur Heart J 2012; 33:2451-96.
14. Turina J, Hess O, Sepulcri F,et al. Spontaneous course ofaortic valve disease. Eur Heart J 1987;8:471-83.
15. Leon MB, Smith CR, Mack M,et al. PARTNER Trial Investigators.Transcatheter aortic-valve implantation for aorticstenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.
16. Smith CR, Leon MB, Mack MJ,et al. PARTNER Trial Investigators.Transcatheter versus surgical aortic-valve replacementin high-risk patients. N Engl J Med 2011;364:2187-98.
17. Sorgato A, Faggiano P, Aurigemma GP,et al. Ventriculararrhythmias in adult aortic stenosis. Prevalence, mechanism,and clinical relevance. Chest 1998;113:482-91.
18. Schwartz LS, Goldfisher J, Sprague GJ,et al. Syncope andsudden death in aortic stenosis. Am J Cardiol 1969;23:647-58.
19. Klein RC. Ventricular arrhythmias in aortic valve disease: analysis of 102 patients. Am J Cardiol 1984; 53:1079-83.
20. Cowan JC, Yusoff K, Moore M,et al. Importance of leadselection in QT interval measurement. Am J Cardiol 1988;61:83-7.
21. Okin PM, Devereux RB, Howard BV,et al. Assessment ofQT interval and QT dispersion for prediction of all-cause andcardiovascular mortality in American Indians. The StrongHeart Study. Circulation 2000; 101:61-6.
22. Gupta P, Patel C, Patel H,et al. T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol 2008;41: 567-74.
23. Zhao X, Xie Z, Chu Y, et al. Association between Tp-e/QT ratio and prognosis in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Clin Cardiol 2012;35: 559-64.
24. Tokatli A, Kilicaslan F, Alis M, et al. Prolonged Tp-eInterval, Tp-e/QT Ratio and Tp-e/QTc Ratio in Patients with Type 2 Diabetes Mellitus. Endocrinol Metab 2016;31:105-12.
25. Zehir R, Karabay CY, Kalayci A, et al. Evaluation of Tpe interval and Tpe/QT ratio in patients with slowcoronary flow. Anatol J Cardiol 2015;15:463-7.
26. Yayla C, Bilgin M, Akboga MK, et al. Evaluation of Tp-E Interval and Tp-E/QT ratio inpatients with aortic stenosis. Ann Noninvasive Electrocardiol 2016;21:287-93.
27. Kahraman S, Dogan A, Kalkan AK, et al. Evaluation of Tp-e interval, Tp-e/QT and Tp-e/QTc ratio in aortic valve stenosis before and after transcatheter aortic valve implantation. J Electrocardiol 2018;51:949-54.
28. Camici PG, Olivotto I, Rimoldi OE. The coronary circulationand blood flow in left ventricular hypertrophy. J Mol Cell Cardiol 2012;52:857-64.
29. Kupari M, Virtanen KS, Turto H, et al. Exclusion of coronaryartery disease by exercise thallium-201 tomography in patientswith aortic valve stenosis. Am J Cardiol 1992;70:635-40.
30. Cameron JS, Kimura S, Jackson-Burns DA, et al. ATP-sensitiveK+ channels are altered in hypertrophied ventricularmyocytes. Am J Physiol 1988;255:1254-8.
31. Tamhane UU, Aneja S, Montgomery D,et al. Association Between Admission Neutrophil toLymphocyte Ratio and Outcomes in Patients With Acute Coronary Syndrome. Am J Cardiol 2008;102:653-57.
32. Cakici M, Cetin M, Dogan A, et al. Neutrophil to lymphocyte ratio predicts poor functional capacity in patients with heart failure. Turk Kardiyol Dern Ars 2014;42:612-20.
33. Kucukseymen S, Cagirci G, Guven R,et al. Is neutrophyl to lymphocyte ratio really auseful marker for all grades of degenerative aortic stenosis? Turk Kardiyol Dern Ars 2017;45:506-13.
34. Leopold JA. Cellular mechanisms of aortic valve calcification. Circ Cardiovasc Interv 2012;5:605-14.