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LEVEL OF GAMMA-GLUTAMYL TRANSFERASE - A NONSPECIFIC OXIDATIVE MARKER - IS INDEPENDENTLY ASSOCIATED WITH HIS-VENTRICULAR INTERVAL PROLONGATION

SPESİFİK OLMAYAN OKSİDATIF BİR BELİRTEÇ OLAN GAMA-GLUTAMİL TRANSFERAZ SEVİYESİ HİS-VENTRİKÜLER ARALIĞI UZAMASI İLE BAĞIMSIZ İLİŞKİLİDİR

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ABSTRACT

Introduction: His-ventricle (H-V) interval is one of the basic measurements of the electrophysiology study (EPS), reflecting conduction time through the His-Purkinje system. Fibrosis and fatty infiltration take a role in the development of H-V interval prolongation. Recent studies claimed that fibrosis in the conduction system could be triggered by oxidative stress. Gamma-glutamyl transferase (GGT) is a non-specific marker of oxidative stress and can be practically evaluated in the clinic. The study aimed to investigate the association of H-V interval prolongation and GGT level.

Methods: The study included 94 consecutive patients (58 women) who underwent clinically indicated EPS with the diagnosis of supraventricular tachycardia. Gamma-glutamyl transferase level was measured with routine laboratory tests before the procedure. Atrial-His, H-V intervals and basal cycle length were measured by performing the standard EPS protocol to patients.

Results: Patient's mean age was 47.9±15.8 years. Participants were analyzed in two groups according to the duration of the H-V interval: ≤ 55 ms (n=66) and >55 ms (n=28). Body-mass index (BMI) (OR 1.153, 95% CI 1.029-1.292, p=0.014) and GGT levels (OR 1.060, 95% CI 1.013-1.108, p=0.012) were independently associated with H-V interval prolongation in multivariate logistic regression analysis.

Conclusion: Gamma-glutamyl transferase and BMI are independently associated with H-V interval prolongation. The relationship of GGT with H-V interval, which extensive studies should confirm, can be a practical aid in the follow-up of patients with infra-His conduction defects.

Keywords: Gamma-glutamyl transferase; His-Ventricle interval; oxidative stress

ÖZET

Giriş: His-ventrikül (H-V) aralığı, His-Purkinje sistemi iletim süresini yansıtır ve elektrofizyolojik çalışmanın (EPS) temel ölçümlerinden biridir. H-V süresi uzamasında fibrozis ve yağ infiltrasyonu rol oynar. Son çalışmalar, iletim sistemindeki fibrozisin oksidatif stres tarafından tetiklenebileceğini iddia etmektedir. Gama-glutamil transferaz (GGT), oksidatif stresin spesifik olmayan bir belirtecidir ve klinikte pratik olarak değerlendirilebilir. Çalışma, H-V interval uzaması ile GGT düzeyi arasındaki ilişkiyi araştırmayı amaçlamıştır.

Yöntemler: Çalışmaya supraventriküler taşikardi tanısı ile klinik olarak endike EPS uygulanan ardışık 94 hasta (58 kadın) dahil edildi. İşlem öncesi rutin laboratuvar tetkikleri ve gama-glutamil transferaz düzeyi ölçüldü. Hastalara standart EPS protokolü uygulanarak Atriyal-His, H-V süreleri ve bazal siklus uzunluğu ölçüldü.

Bulgular: Hastaların yaş ortalaması 47.9±15.8 yıl idi. Katılımcılar H-V süresine göre ≤ 55 ms (n=66) ve >55 ms (n=28) olmak üzere iki grupta analiz edildi. Çok değişkenli lojistik regresyon analizinde vücut kitle indeksi (VKİ) (OR 1,153, %95 CI 1,029-1,292, p=0,014) ve GGT seviyeleri (OR 1,060, %95 CI 1,013-1,108, p=0,012) H-V süresi uzaması ile bağımsız ilişkiliydi.

Sonuç: Gama-glutamil transferaz düzeyi ve VKİ H-V süresi uzamasıyla bağımsız olarak ilişkilidir. Kapsamlı çalışmalarla doğrulanması gereken GGT ve H-V süresi ilişkisi, infra-His iletim kusuru olan hastaların takibinde pratik bir yardımcı olabilir.

Anahtar Kelimeler: Gama-glutamil transferaz; His-ventrikül süresi; Oksidatif stres

INTRODUCTION

Electrophysiological study (EPS) is a specific procedure in diagnosing and treating cardiac arrhythmias. The His-Ventricle (H-V) interval (35-55 msec), which prolongs due to infra-His conduction disturbances, indicates the conduction time from the His bundle to the ventricular myocardium and is routinely measured in the EPS procedure (1). Although its molecular mechanism is unclear, aging and related oxidative stress are thought to cause deterioration in the cardiac conduction system by structural remodeling due to interstitial fibrosis and increased fat depots (2). Oxidative stress exerts its degenerative effect by triggering myocardial fibrosis and scar formation. In addition, oxidative stress disrupts the gap junction, which provides the electrical syncytium in the conduction pathways (3). Imbalance between reactive oxygen species (ROS) generation and clearance results in oxidative stress and inflammation, a critical factor that can result in structural and electrical remodeling of the heart (4). Reactive oxygen species elevation disrupts gap junction conduction, and may results in pacing induced arrhythmia. Although the essential role of ROS in the genesis of arrhythmia is known, the results of

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limited studies with antioxidants are confusing (5).

Gamma-glutamyl transferase (GGT) is an enzyme located on the plasma membranes of various tissues, particularly the hepatocytes. Cellular GGT plays a crucial role in the antioxidant defense system (6). The main task of cellular GGT is to break down the extracellular reduced glutathione and to provide precursor amino acids for intracellular glutathione synthesis. Ectoplasmic GGT supports the cellular supply of glutathione (GSH), one of the most essential antioxidant substances of the cell (7). In contrast, GGT is involved in the formation of ROS in the presence of iron or other transition metals. A potent correlation exists between serum GGT level and cardiovascular risk factors, and studies have demonstrated that GGT may be used as an early and sensitive marker of oxidative stress (8). In fact, it is claimed that the strong relation between GGT and cardiovascular risk factors can be explained by the role of GGT in the oxidative stress process.

Gamma-glutamyl transferase is a nonspecific oxidative stress marker readily accessible in the clinic. Impaired infra-His conduction may cause undesirable cardiac effects on follow-up, and association of this impairment to oxidative stress is still a gap. To our knowledge, no study inspected the relationship between the H-V interval and oxidative markers in the literature. We aimed to investigate whether H-V interval prolongation is associated with GGT level.

MATERIALS AND METHODS

Study Population: The research is a cross-sectional study and was conducted on 94 consecutive patients who underwent EPS diagnosed or pre-diagnosed with supraventricular tachycardia (SVT) between January - June 2020. The electrophysiological study procedure was performed in patients diagnosed with electrocardiography (ECG) or rhythm Holter and prediagnosed patients with SVT based on their symptoms. In the differentiation of symptoms, features such as palpitation frequency and duration, abrupt onset and termination, spread to neck, triggering by stress, vagal maneuver response, response to anti-arrhythmic drugs, whether there was an emergency admission due to palpitations, and a history of syncope were questioned. The principles of the Declaration of Helsinki were taken into account and approval of the study was obtained from the local ethics committee (Recep Tayyip Erdoğan University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee, 13.04.2022, 2022/91).

Treatment of patients with a history of antiarrhythmic drug use was discontinued prior to the procedure for at least four half-lives of the drug. Laboratory data were collected on the morning of hospitalization after at least 12 hours of fasting. The GGT levels were measured by the enzyme assay method. Patients with preexcitation on ECG, a basic rhythm other than sinus rhythm, a history of paroxysmal atrial fibrillation, a history of ablation therapy, congenital heart disease, sinus rhythm >1' AV block, diseases that cause conduction disorders, moderate or severe valve disease, left ventricular systolic dysfunction, cardiac pacemaker or intracardiac defibrillator, chronic renal failure, a history of liver dysfunction or cerebral infarction, malignancy, inflammatory disease, severe comorbid disease were excluded from this study.

Electrophysiological Study: Three 6-Fr2 mm electrode spacing 1.3 mm electrode length quadripolar (The Soloist™, Medtronic) catheter was placed to the high right atrium, his bundle, and right ventricle, and 7-Fr decapolar 2 mm electrode spacing (The Marinr™CS, Medtronic) catheter was placed to the coronary sinus via the femoral vein access. Unfractionated heparin (2500 IU) was administered after the insertion of the catheters. His-ventricle (H-V) interval and basal electrocardiographic recordings were monitored at 100 mm/s through the EP-Tracer® and measured before stimulation. The atrioventricular refractory period (Wenckebachcycle length) was deceived by atrial overdrive pacing. A stimulation protocol was arranged with atrial and ventricular incremental pacing and programmed extra stimulus. Differential diagnosis was made with atrial, ventricular, and His pacing maneuvers in patients with induced SVT.

Statistical Analysis: Study population was analyzed in two groups: H-V interval duration <55 ms and >55 ms. Mean ± standard deviation was used for continuous variables, and percentage was used for categorical variables. Visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk's test) methods were used to determine the normal distribution. Non-normal distributed data were given as median (25-75%). Normally distributed values were compared by the Student's t-test. Non-normally distributed parameters were compared using the Mann-Whitney U-test. Cross tabulations were used to compare the proportions of patients with categorical variables. The Chi-square or Fisher's exact test was used to compare different groups. A p-value <0.05 was considered statistically significant. Parameters that differed significantly between groups in univariate analysis were evaluated with multivariate logistic regression analysis (enter method). To identify independent predictors of H-V prolongation, parameters with p<0.05 in univariate analysis were evaluated by backward multivariate logistic regression analysis (Version 19.0, SPSS, Inc., Chicago, IL).

RESULTS

The mean age of the patients was 47.9 years and 58 (%62) of them were women. Of the 94 patients, 36 (38.2%)

Table 1. Demographic variables of the study population.

Variable	HV≤55 ms (n=66)	HV>55 ms (n=28)	p
Male gender n, %	22 (33)	14 (50)	0.099**
Age	45.6±16.2	53.5±13	0.022***
BMI (kg/m^2)	28.1±5.8	31.8±7.5	0.009***
Diabetes n (%)	4(6.1)	6 (21.4)	0.027#
Hyperlipidemia n (%)	34 (51.5)	15 (53.6)	0.518**
Hypertension n (%)	21 (31.8)	15 (53.6)	0.047**
Smoking n (%)	9 (13.6)	3 (10.7)	0.494#
CAD n (%)	4 (6.1)	7 (25)	0.009#
ASA n (%)	7 (10.6)	11 (39.3)	0.002#
Statin n (%)	2 (3)	5 (17.9)	0.012#
ACEI/ARB n (%)	10 (15.2)	10 (35.7)	0.026#
BCL (ms)	750±116	742±164	0.807
AH interval (ms)	60±16	56±11	0.269***
Wenckebach CL (ms)	319±48	313±44	0.569##
Dual Pathway*	37 (56.1)	20 (71.4)	0.122**
SVT induction*	39 (59.1)	18 (64.1)	0.408**
LV EF	63.4±6.6	63.9±4.8	0.820##
IVS (cm)	1.02±0.22	1.1±0.18	0.918***
Pulse wave (ms)	0.84±0.19	0.91±0.16	0.968***
LVDD (mm)	47.5±2.8	49.9±3.6	0.383***
LVSD (mm)	31.2±2.6	32.5±3.2	0.092##
PR interval (ms)	111.5±16.9	118.5±12.1	0.001***
Heart rate (bpm)	71.8±13.5	74.5±20	0.083***
QRS interval (ms)	106±11.3	109±10.2	0.327##
BUN (mg/dL)	13.4±3.7	16.5±6.2	0.005***
Glucose (mg/dL)	103.5±54.3	113.9±64.2	0.433***
eGFR (ml/dk/1.73 m^2)	99.2±19.9	85.1±22.5	0.010***
Creatinine (mg/dL)	0.77±0.12	0.90±0.43	0.026***
Tot Chol (mg/dL)	205.1±38.3	217.2±65	0.303***
Triglyceride (mg/dL)	144.7±87	164.1±88.3	0.397***
HDL (mg/dL)	52.6±14.4	47.2±10.2	0.110***
LDL (mg/dL)	123.7±33.6	123.9±35.3	0.988##
GGT (U/L)	20.2±10.9	33.2±23.3	0.004***
CRP (mg/L) *	0.24 (0.1-0.67)	0.7 (0.1-0.57)	0.347##
WBC (10^3/uL)	8.1±2.6	7.6±2.3	0.462***
Hemoglobin (g/dL)	13.6±1.5	14.03±1.6	0.313***
Lymphocytes (10^3/uL)	2.6±1	2.5±0.62	0.394##
Monocytes (10^3/uL)	0.59±0.2	0.57±0.16	0.667##

ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, AH: atrial-His interval, ASA: Acetylsalicylic acid, BCL: basal cycle length, BMI: Body mass index, BUN: Blood urea nitrogen, CAD: Coronary artery disease, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, GGT: Gamma glutamyl transferase, HDL: High-density lipoprotein, IVS: interventricular septum, LDL: Low-density lipoprotein, LVDD: Left ventricular diastolic diameter, LVSD: Left ventricular systolic diameter, LV EF: Left ventricular ejection fraction, SVT: Supraventricular tachycardia, Tot Chol: Total cholesterol, WBC: White blood cell count. *Median (25-75%) **Chi-Square test, ***Student's t-test, #Fisher's exact test, ##Mann-Whitney U test

Table 2: Univariate and multivariate logistic regression analysis

	Univariate			Multivariate		
Variable	OR	CI 95%	P	OR	CI 95%	P
BMI*	1.093	1.018-1.074	0.014	1.153	1.029-1.292	0.014
Diabetes*	4.227	1.090-16.39	0.037			
HT*	2.473	1.000-6.115	0.050			
CAD*	5.167	1.374-19.426	0.015			
ASA	5.450	1.833-16.228	0.002			
Statin*	6.950	1.261-38.37	0.026			
ACE/ARB	3.111	1.116-8.670	0.030			
Age*	1.034	1.003-1.067	0.031			
BUN	1.144	1.032-1.269	0.010			
eGFR*	0.970	0.945-0.996	0.023			
Creatinine	10.2	0.7-151.9	0.089			
GGT*	1.049	1.010-1.089	0.013	1.060	1.013-1.108	0.012

ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, ASA: Acetylsalicylic acid, BMI: Body mass index, BUN: Blood urea nitrogen, CAD: Coronary artery disease, eGFR: estimated glomerular filtration rate, GGT: Gamma glutamyl transferase. *Parameters included in multivariate logistic regression (enter method) analysis.

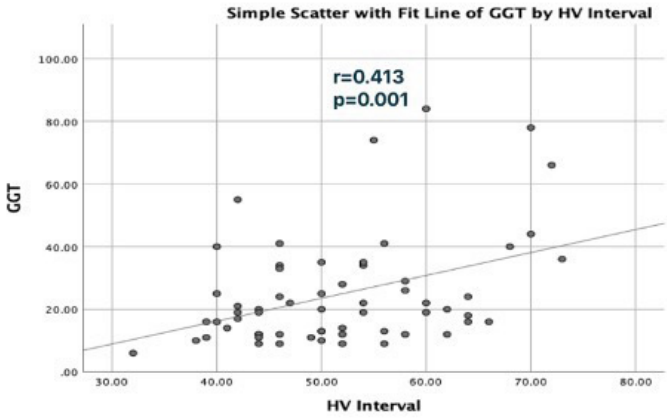

Figure 1: Relationship between GGT and H-V interval.

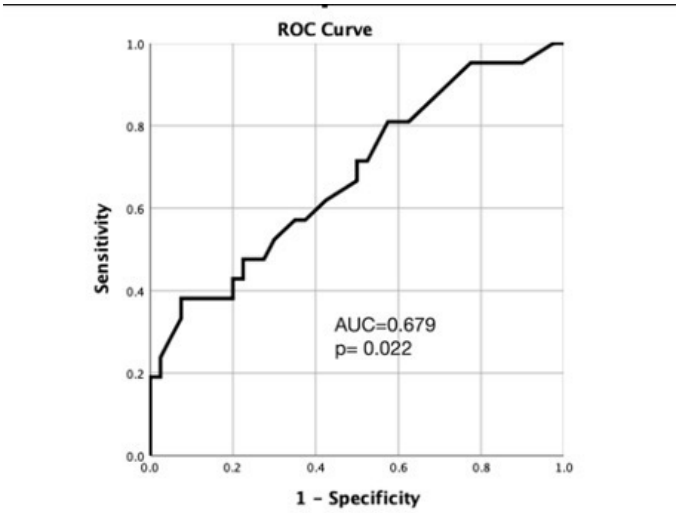

Figure 2: GGT level >16.5 U/L determines HV prolongation with 81% sensitivity and 58% specificity.

presented hypertension (HT), 10 (10.6%) hyperlipidemia, 11 (11.7%) coronary artery disease (CAD), and 10 (10.6%) diabetes mellitus (DM) (Table 1). We analyzed patients in two groups according to the H-V interval duration as ≤ 55 ms (n=66) and >55 ms (n=28). When demographic and laboratory data were assessed by univariate logistic regression analysis, age (p=0.031), HT (p=0.05), CAD (p=0.015), DM (p=0.037), body mass index (BMI) (p=0.014), blood urea nitrogen (p0.001), estimated glomerular filtration rate (eGFR) (p=0.023), and GGT (p=0.013) were associated with H-V interval prolongation. Body mass index (OR 1.153, 95% CI 1.029-1.292, p=0.014) and GGT (OR 1.060, 95% CI 1.013-1.108, p=0.012) were independently associated with H-V interval prolongation in multivariate analysis (Table 2, Figure 1). The GGT level >16.5 U/L determined HV prolongation with 81% sensitivity and 58% specificity (Figure 2).

DISCUSSION

The present study showed that nonspecific oxidative stress marker GGT was independently associated with H-V interval prolongation in SVT patients who underwent EPS. The relationship between H-V interval with GGT levels demonstrated a moderate degree correlation.

Impairment of the balance between ROS and cellular antioxidant mechanism results in oxidative stress. Unstable molecules in the body such as superoxide, hydrogen peroxide, peroxynitrite, and hydroxyl radicals can damage cell structure and signal cascades (9). Increased oxidative stress-mediated by ROS may lead to repolarization and conduction anomalies resulting in cardiac arrhythmias (10). The effect of oxidative stress on arrhythmia has been tried to be elucidated not only by intracellular degeneration but also by unfavorable changes in the biophysical environment of the extracellular matrix (ECM). Oxidative stress increases myocardial fibrosis and scar tissue formation, which causes collagen deposition in the ECM (11). Collagen deposition can reduce the electrical coupling between myocytes. Besides that, gap junction function, which plays a crucial role in the electrical coupling of myocytes, is impaired by oxidative stress (3,12).

The relationship between oxidative stress and arrhythmia has been examined and shown in the literature, principally in atrial fibrillation (AF) patients. The structural and electrophysiological remodeling caused by oxidative stress in the atrial tissue contributes to the AF mechanism (13). Shimano et al. showed that derivatives of reactive oxidative metabolite (DROM) concentrations are higher in patients with persistent AF than in patients with paroxysmal AF (14). The fact that DROM, a marker of oxidative stress, is high in patients with permanent AF confirms the adverse effects of structural and electrophysiological remodeling due to oxidative stress on arrhythmia. Furthermore, although the mechanism is unclear, excess amounts of ROS can cause reentry and focal activity arrhythmias. Disruption of ionic currents in myocyte and ECM due to oxidative stress is in the foreground in the emergence of these arrhythmias (3).
Aging is associated with high levels of oxidative biomolecules that react with free radicals. Free radicals are intermediate oxygen and nitrogen species that attack biomolecules. These intermediates are products of cellular metabolism in which the oxygen used in mitochondrial respiration is converted to reactive oxygen intermediates (15). Oxidative stress is a major cause leading to ageing. As age progress, oxidative stress increases and antioxidant stores diminish. Oxidative stress is involved not only in aging but also in many aging-related diseases (16). In our study, the lack of expected relationship between aging and H-V interval in the multivariate analysis may be due to the fact that the patient's mean age was not advanced.

Gamma-glutamyl transferase performs its main function by metabolizing extracellular reduced GSH to provide precursor amino acids required for intracellular GSH synthesis. Paradoxically, recent experimental studies support that cellular GGT in the presence of iron or transition metal is involved in ROS generation and maybe an early enzyme marker of oxidative stress even within its normal range (8). In the CARDIA study, in which the risk factors for CAD were investigated in young subjects by long-term follow-up, it was suggested that high serum GGT level was associated with increased oxidative stress (17). Furthermore, cellular GGT activity is increased in many tumor types, more prominently in their metastatic forms (18). Based on the findings, it can be suggested that cellular or serum GGT directly or indirectly participates in the development of oxidative stress. The correlation between the GGT levels and the H-V interval in the present study supports the abovementioned findings.

The relationship between obesity and fibrosis is unclear; however, an increase in fibrosis correlates with an increase in BMI secondary to remodeling in the ECM, primarily in adipose tissue (19). Venteclef et al. demonstrated the lineal relationship between epicardial adipose tissue and fibrosis of atrial myocardium in a rat study (20). Increased BMI indicates electrophysiological remodeling, and interstitial fibrosis plays a potent role in the remodeling mechanism (21). Oxidative stress resulting in increased inflammation and fibrosis held responsible for the cardiac conduction abnormalities detected in obesity (22). The relationship between BMI and H-V is consistent with the previous studies.
The H-V interval is one of the basal measures of EPS.

A prolonged H-V interval is often associated with severe myocardial dysfunction and high mortality. Relatively short follow-up periods can detect the progression of H-V space prolongation early. Tests assessing oxidative stress may implicitly help us during follow-up. Various oxidative stress markers can do oxidative damage to lipid, DNA, and protein. However, these biomarkers do not show global body stress, and they are neither cost-effective nor easily applicable in clinical practice (23). Markers such GGT that can be applied easily and widely in clinical practice and which sensitively point to oxidative stress even within the normal laboratory range may be useful in clinical follow-up.

Limitation: Since the study was observational, the possible predictive role of GGT and BMI in follow-up should be confirmed by prospective studies with larger population. The source of oxidative stress and its direct relationship with the H-V interval could not be evaluated. Although it can be considered markers of oxidative stress, GGT can be affected by various clinical conditions. The lack of liver function tests other than GGT in the analysis is one of the limitations of the study.

CONCLUSION

The GGT level and BMI are independently associated with prolongation of H-V interval in SVT patients who underwent EPS. Gamma glutamyl transferase may be used as easily accessible nonspecific oxidative marker in the evaluation and follow-up of H-V interval prolongation associated with oxidative stress and fibrosis. Before using in clinical practice, present data need to be confirmed by prospective studies, supported by follow-up data with larger participation.

Ethics Committee Approval: Approval of the study was obtained from the local ethics committee (Recep Tayyip Erdoğan University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee, 13.04.2022, 2022/91).

Informed Consent: Informed consent was provided from all patients who wanted participated in the study.

Authorship Contributions:
Idea/Concept: AGÖ, AÖ, MÇ, Design: AGÖ, AÖ, MÇ, Supervision: MÇ, Data Collection or Processing: AGÖ, AÖ, MÇ, Analysis or Interpretation: AGÖ, AÖ, MÇ, Literature Search: AGÖ, Writing: AGÖ, AÖ, MÇ, Critical Review: AGÖ, MÇ, References And Fundings: -, Materials: AGÖ.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Miller JM, Zipes DP. Diagnosis of Cardiac Arrhythmias. In Mann DL, Zipes DP, Libby P, Bonow RO, editor. Braunwald's Heart Disease 10th edition. Philadelphia: Elsevier Saunders; 2015. p. 670-1.
2. Tadic M, Cuspidi C. The influence of type 2 diabetes on left atrial remodeling. Clin Cardiol 2015;38:48-55.
3. Sovari AA. Cellular and Molecular Mechanisms of Arrhythmia by Oxidative Stress. Cardiol Res Pract 2016;2016:9656078.
4. Karam BS, Chavez-Moreno A, Koh W, Akar JG, Akar FG. Oxidative stress and inflammation as central mediators of atrial fibrillation in obesity and diabetes. Cardiovasc Diabetol 2017;16:120.
5. Sesso HD, Buring JE, Chriten EG, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. Jama 2008;300:2123-33.
6. Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci 2001;38:263-355.
7. Forman HJ, Liu RM, Tian L. Glutathione cycling in oxidative stress. In Biadasz L, Clerch L, Massaro DJ, editor. Lung Biology in Health and Disease. Vol. 105. Oxygen, gene expression, and cellular function. New York: Marcel Dekker; 1997. p. 99-121.
8. Lee DH, Blomhoff R, Jacobs Jr DR. Is serum gamma glutamyltransferase a marker of oxidative stress? Free Radic Res 2004;38:535-9.
9. El Hadi H, Vettor R, Rossato M. Cardiomyocyte mitochondrial dysfunction in diabetes and its contribution in cardiac arrhythmogenesis. Mitochondrion 2019;46:6-14.
10. Tse G, Yan BP, Chan YWF, Tian XY, Huang Y. Reactive Oxygen Species, Endoplasmic Reticulum Stress and Mitochondrial Dysfunction: The Link with Cardiac Arrhythmogenesis. Front Physiol 2016;7:313.
11. de Bakker JM, van Capelle FJ, Janse MJ, et al. Reentry as a cause of ventricular tachycardia in patients with chronic ischemic heart disease: electrophysiologic and anatomic correlation. Circulation 1988;77:589-606.
12. Morita N, Sovari AA, Xie Y, et al. Increased susceptibility of aged hearts to ventricular fibrillation during oxidative stress. Am J Physiol Heart Circ Physiol 2009;297:1594-605.
13. van Wagoner DR. Oxidative stress and inflammation in atrial fibrillation: role in pathogenesis and potential as a therapeutic target. J Cardiovasc Pharmacol 2008;52:306-13.
14. Shimano M, Shibata R, Inden Y, Yoshida N, Uchikawa T, Tsuji Y. Reactive oxidative metabolites are associated with atrial conduction disturbance in patients with atrial fibrillation. Heart Rhythm 2009;6:935-40.

15. Oliveira BF, Nogueira-Machado JA, Chaves MM. The Role of Oxidative Stress in the Aging Process. Scientific World Journal 2010;10:1121-8.

16. Chaturvedi A, Natarajan A, Sharma V, et al. Association of age-related severity in oxidative stress and blood urea nitrogen levels in patients with dementia: A coastal Karnataka study. Asian j biomed pharm sci 2015;5:6-10.

17. ee DH, Jacobs Jr DR, Gross M, et al. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem 2003;49:1358-66.

18. Maellaro E, Dominici S, Del Bello B, Valentini MA, Pieri L, Perego P. Membrane gamma-glutamyl transpeptidase activity of melanoma cells: effects on cellular H(2)O(2) production, cell surface protein thiol oxidation and NF-kappa B activation status. J Cell Sci 2000;113:2671-8.

19. DeBari MK, Abbott RD. Adipose Tissue Fibrosis: Mechanisms, Models, and Importance. Int J Mol Sci 2020;21:6030.

20. Venteclef N, Guglielmi V, Balse E, et al. Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines. Eur Heart J 2015;36;795-805.

21. Magnani JW, Lopez FL, Soliman EZ, Maclehose RF, Crow RS, Alonso A. P Wave Indices, Obesity, and the Metabolic Syndrome: The Atherosclerosis Risk in Communities Study. Obesity 2012;20:666-72.

22. Pathak RK, Mahajan R, Lau DH, Sanders P. The Implications of Obesity for Cardiac Arrhythmia Mechanisms and Management. Can J Cardiol 2015;31:203-10.

23. Mayne ST. Antioxidant nutrients and chronic disease: use of biomarkers of exposure and oxidative stress status in epidemiologic research. J Nutr 2003;133;933-40.