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The Role of Advanced Glycation End Products in the Etiology of Premature Ventricular Contractions

Prematüre Ventriküler Kasılmaların Etyolojisinde İleri Glikasyon Son Ürünlerinin Rolü

ABSTRACT

Objective: Although the pathophysiological mechanisms responsible for premature ventricular contractions (PVC) are not fully understood, they are primarily thought to occur due to increased automaticity, triggered activity, and reentry. Advanced glycation end products (AGEs) are believed to contribute to these mechanisms. This study aimed to compare AGE levels in patients with and without a PVC rate exceeding 5% in 24-hour Holter monitoring.

Method: Patients were divided into two groups: the PVC case group, defined as having a PVC burden with frequent premature ventricular contractions (≥ 5%) in 24-hour Holter monitoring, and the control group, defined as having rare PVC (< 5%). The patient group consisted of 65 individuals, and the control group also included 65 individuals. For the study, patients' skin AGE levels were measured using a spectrophotometric method.

Results: A significant difference was observed in AGE levels between the two groups. The AGE level was 2.6 (2.1-2.9) AU in the PVC case group, while it was 2.0 (1.7-2.3) AU in the control group (P < 0.001). The receiver operating characteristics curve analysis resulted in an area under the curve value of 0.760 with a 95% confidence interval (CI) of 0.679-0.841 for detecting a PVC burden exceeding 5%. In patients with an AGE level of 2.4 AU, the sensitivity was 61.5%, and the specificity was 80% in detecting a PVC burden above 5%.

Conclusion: Our study showed that AGE levels may be independently and positively associated with a high PVC burden..

Keywords: Advanced glycation end product, arrhythmia, cardiovascular disease, nutrition, premature ventricular contraction

ÖZET

Amaç: Prematüre ventriküler kasılma (PVC) oluşumundan sorumlu patofizyolojik mekanizmalar tam olarak bilinmemekle birlikte, esas olarak artan otomatisite, tetiklenen aktivite ve yeniden giriş nedeniyle meydana geldiği düşünülmektedir. İleri glikasyon son ürünlerinin (AGE) bu mekanizmaları tetiklediği düşünülmektedir. 24 saatlik ritm Holter takibinde PVC oranı %5'in üzerinde olan ve olmayan hastaların AGE seviyelerini karşılaştırmayı amaçladık.

Yöntem: Hastalar iki gruba ayrıldı: 24 saatlik ritm Holter takibinde PVC yükü ≥%5 olanlar PVC vaka grup, PVC yükü <%5 olanlar kontrol grup olarak tanımlandı. Hasta grubu 65 ve kontrol grubu 65 hastadan oluşturuldu. Çalışma için hastaların cilt AGE seviyeleri spektrofotometrik yöntem kullanılarak ölçüldü.

Bulgular: İki grup arasında AGE seviyeleri açısından anlamlı fark gözlendi. PVC vaka grubunda AGE seviyesi 2,6 (2,1-2,9) AU iken, kontrol grubunda AGE seviyesi 2,0 (1,7-2,3) AU idi (P<0,001). Alıcı işletim karakteristik eğrisi analizi, PVC yükünün %5'inin üzerindekileri tespit etme yeteneği için 0,679-0,841'lik %95 güven aralığı ile 0,760'lık bir eğri altında kalan alan değeri ile sonuçlandı. AGE seviyesi 2,4 AU olan hastalarda, %5'in üzerindeki PVC yükünü tespit etmede %61,5'lik bir duyarlılık ve %80'lik bir özgüllüğe sahipti.

Sonuç: Çalışmamız, AGE düzeyinin yüksek PVC yüküyle bağımsız ve pozitif olarak ilişkili olabileceğini göstermiştir.

Anahtar Kelimeler: İleri glikasyon son ürünü, aritmi, kardiyovasküler hastalık, beslenme, erken ventriküler kasılma

Premature ventricular contractions (PVCs) are among the most common rhythm disorders and can be easily detected by electrocardiography (ECG). PVCs are characterized by beats with a distinct morphology and a duration greater than 120

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KLİNİK ÇALIŞMA

Alkame Akgümüş[1]

Ali Duygu[2]

[1]*Department of Cardiology, Bandırma Onyedi Eylül University, Faculty of Medicine, Balıkesir, Türkiye*
[2]*Department of Cardiology, Bandırma Training and Research Hospital, Balıkesir, Türkiye*

Corresponding author:
Alkame Akgümüş
✉ aakgumus@bandirma.edu.tr

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milliseconds, which is longer than the normal QRS complex on the ECG. The T wave following a PVC is in the opposite direction to the QRS complex. The clinical spectrum of PVC is broad; while some cases are completely asymptomatic, others may present with symptoms such as dyspnea, syncope, or presyncope.[1] The most common symptoms include chest discomfort and palpitations, often described as strong or irregular heartbeats. Other symptoms related to heart failure may also be observed in patients who develop PVC-induced cardiomyopathy and whose ejection fraction (EF) falls below 50%.[1,2]

Determination of PVC burden through ambulatory ECG monitoring plays a significant role in treatment and prognostic evaluation. The PVC burden is expressed as the ratio of the number of PVCs to the total heart rate over a 24-hour period, represented as a percentage. In one study, the frequency of PVCs was found to be 4% in healthy individuals, while another study reported that at least one PVC was observed in 1.8% of participants in 12-lead ECG recordings. These studies also indicated that the frequency of PVCs increases with advanced age, the presence of hypertension, male sex, and structural heart disease.[3,4] Frequent PVCs are typically symptomatic and are also known to cause arrhythmia-induced cardiomyopathy. A 24-hour PVC burden of less than 5% is classified as low, between 5% and 20% as medium, and greater than 20% as high.[5] In general, PVC-induced cardiomyopathy is observed when the frequency of PVCs over a 24-hour period exceeds 10–25% of total heartbeats.[6,7]

The pathophysiological mechanisms responsible for PVC formation are not fully understood; however, it is believed to result primarily from increased automaticity, triggered activity, and reentry. Ventricular arrhythmias occurring in a structurally normal heart are considered idiopathic. The mechanism responsible for the formation of idiopathic PVCs is primarily triggered activity.[8]

Advanced glycation end products (AGEs), which are formed as a result of the non-enzymatic glycation of biomolecules, play a role in the pathophysiology of many diseases by altering the physical, chemical, and metabolic structure of the organism, negatively affecting disease prognosis.[9] AGEs contribute to cardiovascular diseases through two mechanisms: receptor-mediated and non-receptor-mediated interactions. They activate signaling mechanisms in various cells by binding to receptors on cell surfaces.[10] A recent study noted that inhibiting AGE formation reduced susceptibility to tachyarrhythmias in diabetic animals.[11]

In our study, we examined AGEs that may be associated with the formation of PVCs, a common rhythm disturbance in heart disease, including in healthy individuals. This study aimed to compare AGE levels in patients with and without a PVC rate exceeding 5%.

Materials and Methods

The study population consisted of a patient group with more than 5% PVCs detected in ECG and 24-hour Rhythm Holter electrocardiography follow-up, and a control group with less than 5% PVCs detected in previous hospital admissions and new admissions. The patient group included 65 individuals, and the control group included 65 individuals.

ABBREVIATIONS

AF	Autofluorescence
AGEs	Advanced glycation end products
ATP	Adenosine triphosphate
ECG	Electrocardiography
EF	Ejection fraction
NF-κB	Nuclear factor kappa B
PVC	Premature ventricular contractions
ROS	Reactive oxygen species
RVOT	Right ventricular outflow tract
SR	Sarcoplasmic reticulum

The inclusion criteria were as follows:

1. Patients with a total PVC load of 5% or more during 24-hour Holter electrocardiography monitoring.
2. Patients whose 12-lead ECG records indicate idiopathic PVC, particularly those with outflow tract PVC.
3. Patients over the age of 18.
4. The control group consisted of adults with less than 5% PVC detected during ECG and 24-hour Rhythm Holter electrocardiography monitoring.

The exclusion criteria for this study were as follows:

1. Patients with coronary ischemia detected by clinical and laboratory findings.
2. Patients with a positive exercise test.
3. Patients with a history of heart valve disease.
4. Patients with heart failure.
5. Patients with structural heart disease.
6. Patients with arrhythmias other than PVC.

For the study, skin AGE levels were measured using the spectrophotometric method. Spectrophotometric measurement was performed non-invasively on the inner surface of the forearm using an AGE Reader (DiagnOptics, Groningen, The Netherlands) by taking three skin measurements and averaging them. Skin autofluorescence (AF) was assessed using the AGE Reader (DiagnOptics Technologies BV, Groningen, The Netherlands). The AGE Reader is a non-invasive mobile device that uses the characteristic fluorescence properties of specific AGEs to estimate their accumulation levels in the skin. The AGE Reader illuminates a 4 cm2 skin surface through an excitation light source with a peak excitation of 370 nm. Emission light (fluorescence at a wavelength of 420-600 nm) and excitation light reflected from the skin (at a wavelength of 300-420 nm) are measured using a spectrometer. Skin AF is calculated as the ratio between emission light and reflected excitation light, multiplied by 100, and expressed in arbitrary units. Echocardiographic data of the patients were recorded. Since this study was a case-control study, the same measurements were taken from healthy individuals.

Demographic, clinical, and laboratory values, as well as electrocardiographic and 24-hour Holter electrocardiography recording data, were collected from patient files. The study protocol was approved by Bandırma Onyedi Eylül University Health Sciences Non-Interventional Research Ethics Committee (Approval Number: 762, Date: 06.05.2024).

Table 1. Patient Demographics and Advanced Glycation End Products (AGEs) Values

Variables	Case Group	Control Group	P
Number of patients	65	65	
Age, years	63.0 (53.0–69.0)	56.0 (49.5–70.5)	0.10
Sex (male), n (%)	29 (44.6)	19 (29.2)	0.07
Smoking, n (%)	10 (15.4)	15 (23.1)	0.27
Diabetes mellitus, n (%)	11 (16.9)	15 (23.1)	0.38
Hypertension, n (%)	31 (47.7)	32 (49.2)	0.86
CAD, n (%)	7 (10.8)	3 (4.6)	0.19
Hyperlipidemia, n (%)	7 (10.8)	14 (21.5)	0.09
Ejection fraction	60.0 (60.0–60.0)	60.0 (60.0–60.0)	0.19
BMI (kg/m^2)	26.1 (23.7–30.9)	26.3 (23.9–28.3)	0.76
24-hour PVC burden	12.2 (7.0–19.5)	–	< **0.001**
AGEs (AU)	2.6 (2.1–2.9)	2.0 (1.7–2.3)	< **0.001**

AGEs, Advanced Glycation End Products; BMI, Body Mass Index; CAD, Coronary Artery Disease; PVC, Premature Ventricular Contraction.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Version 23.0 for Windows (IBM Corp., Armonk, NY, USD). The conformity of the variables to a normal distribution was examined using both visual methods (histograms and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). For group comparisons, parametric and non-parametric tests were applied based on data distribution. Student's t-test was used for independent samples with normally distributed parameters, while the Mann-Whitney U test was used for non-normally distributed variables. To assess the relationship between the presence of PVCs and AGE values, receiver operating characteristic (ROC) curve analysis was performed, and sensitivity and specificity values were determined. A significance level of $P < 0.05$ was used, and results were summarized with 95% confidence interval values. G-Power software (version 3.1.9.7) was used to determine the minimum sample size. The selected parameters included t-tests for the difference between two independent means (matched pairs) with an a priori computation of the required sample size based on alpha (α) error probability, power, and effect size. When the alpha error probability (α err prob) was set at 0.05, power (1-β err prob) at 0.80, and effect size at 0.45, it was determined that at least 62 participants were required for each group (actual power = 80.1%).

Results

In our study, 65 patients had a PVC burden of more than 5%, while 65 patients had a PVC burden of less than 5%, as recorded in the 24-hour rhythm Holter electrocardiography. No statistically significant differences were observed between the groups in terms of baseline demographic and clinical characteristics (Table 1). Additionally, no significant differences were found between the patient groups regarding comorbidities such as diabetes mellitus, coronary artery disease, hypertension, and hyperlipidemia. The body mass index of patients in both groups was similar. According to the 24-hour ECG Holter recordings of the case group, the median PVC burden was 12.2% (7.0-19.5). A significant difference was observed between the two groups in terms of AGE levels. The median AGE level was 2.6 (2.1-2.9) AU in the PVC-positive case group, whereas it was 2.0 (1.7-2.3) AU in the control group ($P < 0.001$). The AGE levels of the groups are shown in Figure 1. Among the patients, 51 had PVCs originating from the left ventricle, while 14 had PVCs originating from the right ventricle. The median AGE level of patients with PVCs originating from the left ventricle was 2.6 (2.1-3.0) AU, while the median AGE level of those with PVCs originating from the right ventricle was 2.35 (2.0-2.6). No statistically significant difference was observed between these groups ($P = 0.125$).

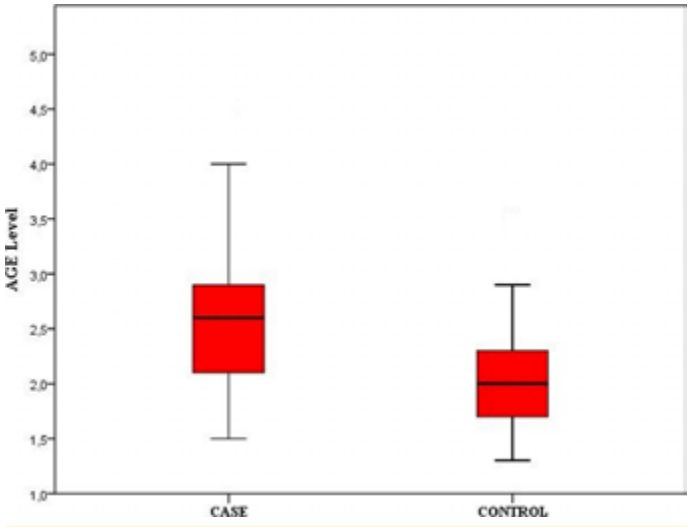

Figure 1. Box plot graph depicting advanced glycation end product (AGE) levels in the patient and control groups.

Receiver operating characteristic curve analysis yielded an area under the curve (AUC) value of 0.760 with a 95% confidence interval (CI) of 0.679-0.841 for detecting a PVC burden above 5%. In patients with an AGE level of 2.4 AU, sensitivity was 61.5% and specificity was 80% for detecting a PVC burden exceeding 5% (Figure 2).

Table 2. Univariate and Multivariate Logistic Regression Analysis for Risk Factors Predicting Premature Ventricular Contraction (PVC) Burden Above 5%

	Univariate	Multivariate
Dependent: PVC	**OR (95% Confidence Interval)**	**OR (95% Confidence Interval)**
Age, years	1.01 (0.98–1.04, P = 0.34)	
Hyperlipidemia	2.27 (0.85–6.07, P = 0.10)	
Hypertension	1.06 (0.53–2.12, P = 0.86)	
CAD	0.40 (0.10–1.62, P = 0.20)	
Diabetes mellitus	0.68 (0.28–1.62, P = 0.38)	
Ejection fraction	0.91 (0.82–1.01, P = 0.07)	0.97 (0.85–1.09, P = 0.58)
Smoking	1.65 (0.68–4.01, P = 0.27)	
AGE level	7.50 (3.16–17.76, P < 0.001)	7.26 (3.03–17.38, P < 0.001)

AGEs, Advanced Glycation End Products; CAD, Coronary Artery Disease; OR, Odds Ratio; PVC, Premature Ventricular Contraction.

After performing univariate logistic regression analysis, multivariate logistic regression analysis was conducted, considering EF and AGE level as risk factors. In the multivariate logistic regression analysis, AGE level (odds ratio [OR]: 7.26, 95% CI: 3.03–17.38, P < 0.001) was identified as an independent predictor of a PVC burden above 5% (Table 2).

Discussion

In recent years, the consumption of processed foods has increased significantly, leading to a higher intake of sugar and fat in the diet. Changes in eating habits have also contributed to increased exposure to AGEs. Currently, it has been reported that dietary AGEs are associated with various diseases, including the development of insulin resistance and diabetes.[12] In our study, we investigated whether AGEs play a role in the etiology of PVC, which have an unknown cause and are not related to structural heart disease.

AGEs are a heterogeneous group of compounds formed as a result of the non-enzymatic glycation of free amino groups in proteins, lipoproteins, or nucleic acids and the carbonyl groups of reducing sugars.[13] This reaction progresses gradually through different stages, leading to cellular changes. In addition to AGEs produced in the body, these compounds can also be ingested through dietary sources. AGEs are naturally present in raw animal-derived foods, and their formation increases during cooking. In particular, grilling, frying, and roasting are known to enhance AGE formation. The primary route of AGE elimination from the body is via the kidneys.[13,14] The accumulation of AGEs in the body can lead to detrimental effects by altering the physical, chemical, and metabolic structure of the organism. AGEs play a role in the pathophysiology of many diseases and can negatively impact disease prognosis.[15] Previous studies have demonstrated that AGEs contribute to the pathogenesis of atherosclerosis, neurodegenerative diseases, and diabetic complications.[16]

Although AGE levels can be measured in peripheral blood samples and urine, the optimal measurement method remains unclear. The levels of AGEs in peripheral blood may not accurately reflect their accumulation in tissues. Measuring AGEs with fluorescent properties in the skin provides more accurate data and can be performed non-invasively.[17,18] In our study, skin AGE levels were measured using the spectrophotometric method, which is more practical and allows for a relatively more reliable assessment of AGE accumulation.

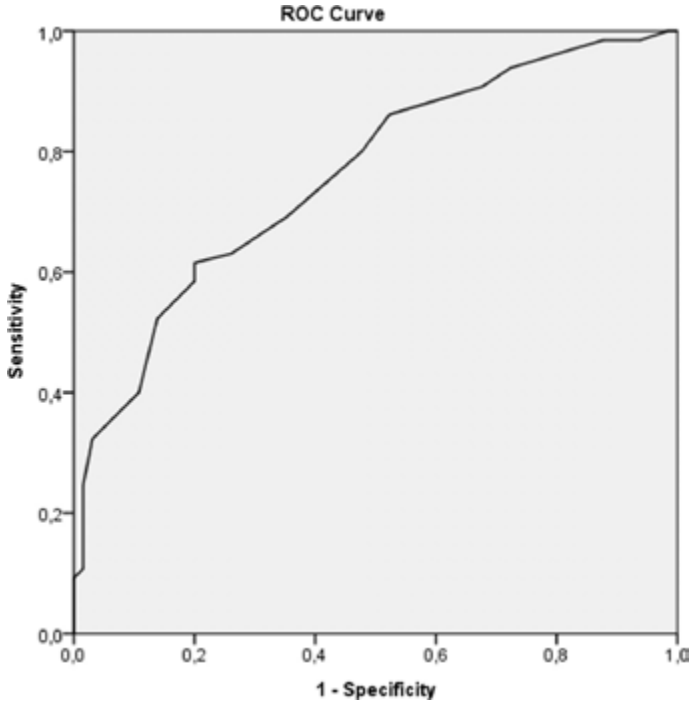

Figure 2. Receiver operating characteristic (ROC) curve analysis of advanced glycation end product (AGE) levels for predicting a premature ventricular contraction burden of ≥ 5%.

AGEs disrupt the structure of extracellular proteins, leading to alterations in the normal structure and function of tissues while also triggering an inflammatory response. These changes in cell-matrix interactions result in the loss of endothelial function and a decrease in nitric oxide production by endothelial cells.[19] Intracellular accumulation of AGEs causes protein misfolding in the endoplasmic reticulum, leading to dysfunction. The excitation-contraction relationship in cardiac myocytes is regulated by intracellular calcium (Ca^{2+}) transport mechanisms. The diastole process is crucial for the adequate filling of the ventricles with blood. For the relaxation phase, which occurs during diastole after the contraction of the heart, intracellular Ca^{2+} must be removed. The Na^{+}-Ca^{2+} exchanger on the cell membrane and the sarcoendoplasmic Ca^{2+}-ATPase

(SERCA2a) mechanisms on the sarcoplasmic reticulum (SR) play a fundamental role in Ca^{2+} removal. We hypothesized that structural and functional alterations in SERCA2a and the Na^{+}-Ca^{2+} exchanger caused by AGEs in cardiac myocytes may disrupt intracellular Ca^{2+} homeostasis, leading to disturbances in action potential phases and the development of arrhythmias in cardiac myocytes. AGEs can also reduce adenosine triphosphate (ATP) synthesis and increase the production of superoxide and reactive oxygen species (ROS) by binding to mitochondrial proteins within the cell. Additionally, AGEs are known to reduce the activity of antioxidant enzymes such as glutathione peroxidase and glutathione reductase.[20] In receptor-mediated interactions, AGEs bind to AGE receptors (RAGE), which are cell surface receptors, altering tissue function and mechanical properties and contributing to the development of cardiovascular disease.[21] AGE-RAGE binding has been shown to induce oxidative stress and activate nuclear factor kappa B (NF-κB) transcription. Activation of NF-κB stimulates signaling cascades that increase pro-inflammatory cytokines and ROS production while also promoting fibrotic and thrombotic pathways.[12]

Although the exact mechanism of PVCs is unclear, multiple mechanisms are believed to be responsible, including triggered activity, increased automaticity, and reentry. The primary mechanism responsible for the formation of idiopathic PVCs is mostly triggered activity.[8] Most PVCs in structurally normal hearts originate from triggered activity due to late afterdepolarizations. Late afterdepolarization occurs due to an excessive increase in diastolic intracellular Ca^{2+} during phase 4 of the action potential. Intracellular AGEs disrupt calcium homeostasis by cross-linking to ryanodine receptors and SERCA2a.[22] Ryanodine receptor 2, the cardiac muscle-specific isoform responsible for Ca^{2+} release from the SR, is highly susceptible to oxidative stress. Previous studies have demonstrated that ROS induce sulfhydryl oxidation of the ryanodine receptor, leading to intracellular Ca^{2+} leakage from the SR and an increased risk of ventricular arrhythmias.[23] Additionally, oxidation of the sulfhydryl groups of SERCA2a, which is responsible for Ca^{2+} removal from the cytoplasm, results in elevated intracellular Ca^{2+} levels and prolongation of the action potential.[24,25] Dysfunction of the Na^{+}/Ca^{2+} exchanger, a sarcolemmal protein involved in intracellular Ca^{2+} extrusion, caused by ROS may further contribute to delayed afterdepolarization and arrhythmia. As a result of these alterations in Ca^{2+} homeostasis, intracellular calcium levels increase, leading to the activation of calcium-dependent cytosolic proteases. These proteases convert intracellular hypoxanthine dehydrogenase into xanthine oxidase, ultimately contributing to further superoxide radical formation. Elevated intracellular Ca^{2+} levels may also stimulate ROS production through the activation of phospholipase C and arachidonic acid metabolism.[23] A study conducted by Bérubé et al.[26] found that oxidative stress may also contribute to ventricular arrhythmias by affecting sarcolemmal ion channels, leading to disruptions in Na^{+} and K^{+} homeostasis. Based on these findings, we hypothesized that increased intracellular Ca^{2+} levels in cardiac myocytes may contribute to PVCs by altering Na and K metabolism.

We hypothesized that AGEs might also contribute to pathophysiology through increased automaticity. While cells in the His-Purkinje system spontaneously depolarize at a rate of 15-60 beats per minute, ventricular myocardial cells generally do not exhibit spontaneous diastolic depolarization or automaticity.[27] However, AGEs increase intracellular Ca^{2+} levels by altering Ca^{2+} metabolism within the cell and may contribute to PVC formation by enhancing automaticity. This occurs through a positive shift in the transmembrane potential during phase 4, facilitating a new depolarization. The mechanism of abnormal automaticity in cardiomyocytes is primarily linked to intracellular Ca^{2+} metabolism. The cellular Ca^{2+} cycle is intricately regulated by multiple intracellular compartments, including the cell membrane, SR, and mitochondria.[28] It is known that AGEs affect the Na^{+}/Ca^{2+} exchanger, SERCA2a, and the ryanodine receptor in the cell membrane, thereby disrupting Ca^{2+} metabolism.[22,23] A study by Chen et al.[22] on rabbits demonstrated that AGEs cause mitochondrial dysfunction in the right ventricular outflow tract (RVOT) via ROS and may trigger ventricular arrhythmias by inducing Na^{+} and Ca^{2+} leakage. Similarly, Ward et al.[29] found that AGEs-RAGE interactions influence mitochondrial function. Furthermore, Xie et al.[30] demonstrated that disruptions in intracellular Ca^{2+} metabolism due to mitochondrial and sarcolemmal dysfunction may increase automaticity in the ventricular myocardium. These findings support our hypothesis that AGEs may contribute to pathophysiology through increased automaticity.

There are three main characteristics that define reentry: the presence of two separate conduction pathways, one with a conduction block and the other with a slow conduction zone.[31] Raposeiras-Roubín et al.[32] demonstrated that AGEs alter the structure and function of extracellular proteins such as type I collagen and elastin, potentially leading to atrial fibrosis through the effects of pro-inflammatory cytokines and ROS. Similarly, AGEs may contribute to the formation of fibrotic islands in the ventricular myocardium due to inflammation and oxidative stress, resembling atrial fibrosis. Functionally heterogeneous areas develop as a result of the varying electrophysiological properties between healthy myocardium, dense scar tissue, and intermediate regions. Differences in action potential duration and conduction velocity variability within these heterogeneous regions may promote the formation of reentrant mechanisms. Thus, AGEs may facilitate PVC formation through the reentry mechanism.[33,34]

Conclusion

Based on our study, we think that AGEs, which have become more prevalent due to advancements in the food industry and an increasingly sedentary lifestyle, may contribute to the development of cardiovascular diseases, a major health concern in modern society. Although the precise mechanism underlying PVCs is not fully understood, multiple mechanisms, including triggered activity, increased automaticity, and reentry, are believed to be involved. Given the detrimental effects of AGEs observed in our study, we hypothesize that AGEs may contribute to all three mechanisms and play a role in the etiology of PVCs. Beyond increasing mortality, arrhythmias such as PVCs can lead to anxiety, stress, and heart failure in affected individuals. Thus, AGEs should not be regarded as benign. According to our study findings, modifications in dietary habits and a preference for foods with lower AGE content may reduce hospital admissions related to PVCs, decrease the need for and dosage of antiarrhythmic medications, and, most importantly, lower rates of heart failure and mortality.

Ethics Committee Approval: Ethics committee approval was obtained from Bandırma Onyedi Eylül University Health Sciences Non-Interventional Research Ethics Committee (Approval Number: 762, Date: 06.05.2024).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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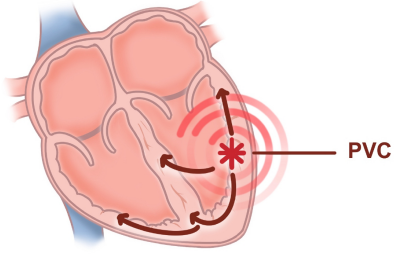
The Role of Advanced Glycation End Products in the Etiology of Premature Ventricular Contractions

This study aimed to compare AGE* levels in patients with and without a PVC** rate exceeding 5% in 24-hour Holter monitoring.

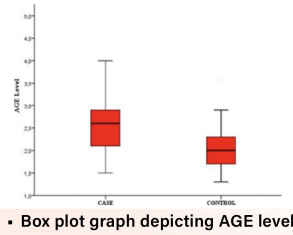
PVC Case Group
n=65
(PVC Burden ≥ 5%)

Control Group
n=65
(PVC Burden < 5%)

AGE Level (AU)	2.6 (2.1-2.9)	vs	2.0 (1.7-2.3)	p<0.001



- Patients' skin AGE levels were measured using a spectrophotometric method.
- The ROC curve analysis resulted in an AUC value of 0.760 with a 95% CI of 0.679-0.841 for detecting a PVC burden exceeding 5%.



- Box plot graph depicting AGE levels in the patient and control groups.

Our study showed that AGE levels may be independently and positively associated with a high PVC burden.

*AGE:Advanced glycation end products, **PVC: premature ventricular contractions

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