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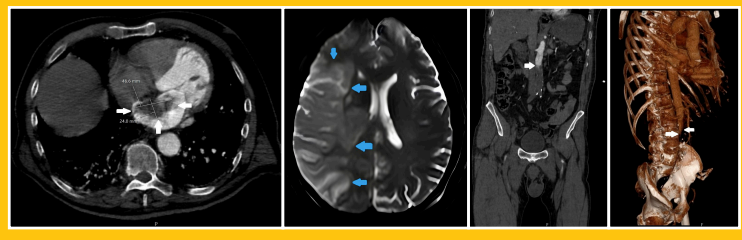

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Comparison of Meteorin-like Protein Infusion and Moderate-Intensity Exercise on Cardiac Mast Cell and Plasma Cell Dynamics and Musclin Levels in Female Rats

Dişi Sıçanlarda Kardiyak Mast Hücre ve Plazma Hücre Dinamikleri ve Musklin Seviyeleri Üzerinde Meteorin-Like Protein İnfüzyonu ile Orta Şiddetli Egzersizin Karşılaştırılması

ABSTRACT

Objective: Moderate-intensity exercise modulates the immunological response in cardiac tissue. Meteorin-like protein (METRNL) is a myokine secreted by muscle cells during exercise and is involved in immune response regulation. However, the effects of metrnl on mast cells and plasma cells in cardiac tissue are not fully understood. This study was designed to assess the effects of exogenous metrnl infusion on the cardiac mast cells and plasma cells. In addition, serum levels of musclin, an exercise-responsive factor, were evaluated during the effects of moderate-intensity exercise on cardiac immune cells.

Method: Twenty-seven female rats were randomly divided into three groups (n = 9 each): control (deionized water), exercise (moderate-intensity swimming exercise) and metrnl (1 µg/day). For histological studies, hematoxylin-eosin, toluidine blue and methyl green-pyronin staining were performed on heart tissues. Musclin levels were measured in serum samples using the ELISA method.

Results: Metrnl infusion increased cardiac mast cell and plasma cell numbers in female rats like moderate-intensity exercise. In addition, the increase in cardiac mast cell count was greater in the exercise group, whereas musclin concentration decreased in female rats subjected to moderate-intensity exercise.

Conclusion: Our data suggest that moderate-intensity exercise's effects on the cardiac immune system may be mediated by musclin downregulation and metrnl-dependent upregulation of cardiac mast cells and plasma cells. Thus, exercise-induced metrnl may affect the cardiac immune response by modulating cardiac immune cells.

Keywords: Exercise, heart, mast cell, meteorin-like protein, musclin (osteocrin), plasma cell

ÖZET

Amaç: Orta şiddetli egzersiz kalp dokusunda immünolojik cevabı modüle eder. Meteorin-like protein (metrnl), egzersiz sırasında kas hücreleri tarafından salgılanan bir miyokindir ve bağışıklık yanıtının düzenlenmesinde rol oynar. Ancak, metrnl'nin kardiyak dokuda mast hücre ve plazma hücresi üzerindeki etkileri tam olarak bilinmemektedir. Bu çalışma, ekzojen metrnl infüzyonunun kardiyak mast hücre ve plazma hücresi üzerindeki etkilerini değerlendirmek için tasarlandı. Ayrıca, orta şiddetli egzersizin kardiyak bağışıklık hücreleri üzerindeki etkileri sırasında egzersize yanıt veren bir faktör olan musklinin serum seviyeleri değerlendirildi.

Yöntem: 27 adet dişi sıçan rastgele 3 gruba ayrıldı (n = 9, her grupta): kontrol (deiyonize su), egzersiz (orta şiddetli yüzme egzersizi) ve metrnl (1 µg/gün). Histolojik çalışmalar için kalp dokularında hematoksilen-eozin, toluidine blue ve metil green-pironin boyaması yapıldı. Musklin seviyeleri serum örneklerinde ELISA yöntemi kullanılarak ölçüldü.

Bulgular: Dişi sıçanlarda metrnl infüzyonu orta şiddetli egzersiz gibi kardiyak mast hücre ve plazma hücre sayılarını artırdı. Ayrıca, kardiyak mast hücre sayısındaki artış egzersiz grubunda daha fazlaydı, buna karşın orta şiddetli egzersize tabi tutulan dişi sıçanlarda musklin konsantrasyonu azaldı.

Sonuç: Özetle, verilerimiz orta şiddetli egzersizin kardiyak immün sistem üzerindeki etkilerine musklinin downregülasyonunun ve metrnl bağımlı kardiyak mast hücre ve plazma hücrelerinin upregülasyonunun aracılık edilebileceğini göstermektedir. Bu nedenle, egzersiz indüklü metrnl, kardiyak bağışıklık hücrelerini modüle ederek kardiyak immün yanıtını etkileyebilir.

Anahtar Kelimeler: Egzersiz, kalp, mast hücresi, meteorin-like protein, musklin (osteokrin), plazma hücresi

ORIGINAL ARTICLE
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The immune system is crucial for preserving health and is an extremely complex organization of cells and molecules with specialized roles in defending against infection.[1] The innate and adaptive arms of immunity are in constant interaction and work in coordination with each other. The innate immune cells include granulocytes, macrophages, dendritic cells and mast cells, which respond rapidly, while adaptive immune cells, consisting of B and T cells, have a delayed response.[2] Mechanistically, it has been demonstrated that both innate and adaptive immunity have a part to play in cardiac physiology.[3]

Mast cells, regarded as one of the fundamental components of the immune system, are implicated in various disorders, including allergy, asthma, anaphylaxis, as well as gastrointestinal and cardiovascular diseases. In addition, mast cells also regulate a number of normal physiological processes such as vasodilation and angiogenesis.[4] The bone marrow's pluripotent progenitor cells are the source of mast cells and mast cells are present in various organs and tissues such as skin, airways, gastrointestinal tract, testis, ovary and heart.[5] Aside from mast cells, a distinct variety of immune cells, such as resident macrophages, patrolling monocytes, dendritic cells, T cells, B cells and plasma cells, are also present in the healthy, homeostatic myocardium.[6]

Terminal differentiation of B cells generates plasma cells that secrete large quantities of antibodies during humoral immune response. Thus, plasma cells are vital effector cells of humoral immunity. Found mostly in connective tissue and very rarely in the blood, long-lived plasma cells exist primarily in the bone marrow, but they are also found in various lymphoid organs throughout the body and, in disease states, in non-lymphoid organs.[7]

Systemic exposure to repeated exercise stimuli leads to long-term adaptations in various tissues, which triggers a number of well-known effects of exercise. These include greater vascularization and mitochondrial biogenesis, improved adipose and liver tissue processing of substrates, as well as improved cardiac and immune cell function.[8] Based on the relationship between exercise, immunological response and health, it is known that exercise strengthens the immune system, by lowering oxidative stress linked to inflammatory marker levels and enhancing the body's immunological response.[9] Exercise causes the immune system to undergo major physiological changes and these changes vary greatly depending on the nature and intensity of the exercise. Exercise-induced immunological alterations are caused by a variety of multifactorial pathways, including several neuroendocrine variables and immune cell function.[1] For example, the human immune system is greatly impacted by low-intensity physical exercise since it can greatly boost immune cell proliferation and inactivation capacity.[10] It has been shown that an increased release of various myokines due to physical exercise, such as interleukin-6 (IL-6), can neutralize inflammation by attracting other immune cells and producing anti-inflammatory cytokines. At present, it has been proposed that myokines could mediate the health benefits of exercise and, in particular, that they might help prevent chronic diseases such as diabetes and cardiovascular disease, that are linked to low-grade inflammation.[11] However, despite the immunomodulatory effects of exercise, the fundamental mechanisms that support cardiovascular health are not fully understood. Recognizing the key determinants by which exercise modulates immune function could potentially provide new therapeutic targets for the treatment of cardiovascular disease.

ABBREVIATIONS

ANOVA	One-way analysis of variance
ELISA	Enzyme-linked immunosorbent assay
SEM	Standard error of the mean

Meteorin-like protein (metrnl) has been identified as a myokine, adipokine and cardiokine expressed in a variety of tissues such as skeletal muscle, adipose tissue and heart. Metrnl is a key component of muscle metabolism, the maintenance of systemic energy balance and inflammatory immune regulations and is released by muscle cells during exercise. It has been reported that increased metrnl release resulting from moderate-intensity physical activity, reduced inflammation and pyroptosis. Accordingly, metrnl has been noted to have cardioprotective effects by affecting systemic inflammation.[12,13] However, the effects of metrnl on mast cells and plasma cells in the heart tissue, regarded as an exercise mediator, are not fully known.

Musclin, another name for osteocrin, is a myokine that responds to exercise and a peptide belonging to the natriuretic peptide family. The expression of musclin varies depending on nutritional changes (like obesity), diabetes, cold exposure and exercise intervention. Accordingly, it has been shown that musclin levels are induced or downregulated by exercise. It has been demonstrated that musclin is involved in several metabolic processes, such as mediating insulin-dependent glucose metabolism, promoting mitochondrial biogenesis and regulating cardiovascular homeostasis, by attenuating inflammation.[14,15] However, the relationship between the circulating musclin level and the mast cells and plasma cells, which are important components of the immune system during exercise, is not clear.

To investigate the possible role of exercise-responsive metrnl and musclin in the effects of moderate-intensity exercise on cardiac immune response, this study aimed to assess the effects of metrnl on the mast cell and plasma cell counts in the heart tissues and serum musclin levels, in comparison with moderate-intensity exercise in female rats.

Materials and Methods

This study was approved by the Animal Experimental Ethics Committee of Fırat University (Approval Number: 2023/16-06, Date: 20.09.2023) and conducted in accordance with the Declaration of Helsinki. Artificial intelligence-assisted technologies were not used in the production of this study.

Animals

This study used exclusively female rats, since the immune system works more efficiently in females than in males.[16] Estrous cycle monitoring was performed on 40 Sprague-Dawley rats (200-250 g, 2-3-month-old, obtained from Fırat University's Experimental Animals Unit) for 10 days. At the end of the 10-day estrous cycle monitoring, a total of 27 rats determined to have regular estrous cycles were included in the study. The animals were housed

(three rats per cage) at a constant temperature (21 ± 1 °C) and humidity (50-55%) with a 12/12h light/dark cycle and food and water were provided ad libitum. The National Institutes of Health Guide for the Care and Use of Laboratory Animals was followed in all of the experiments.

Experimental Design

The animals were randomly split into three groups, each group containing nine rats: 1) Control group: Animals received intraperitoneal (i.p.) injections of deionized water for 19 consecutive days 2) Metrnl group: Animals were given the i.p. injections of metrnl in a concentration of 1 µg/day for about 19 days.[17] 3) Exercise group: Animals were submitted to a moderate-intensity swimming exercise (30 minutes/day, 5 days/week) for about 19 days.[18]

Swimming Exercise Protocol

The exercise group was given a swimming exercise consisting of two stages: swimming adaptation and swimming exercise. All animals in the exercise group were first allowed to swim freely in a swimming tank for five minutes per day for one week, to ensure adaptation to the exercise before starting swimming training. After the swimming adaptation period was completed, the animals were given swimming exercise for 30 minutes per day, five days per week for an average of 19 days. During the experiment, all swimming exercises were performed at 13:00-15:00 in the swimming tanks, which were 25 cm in diameter, 60 cm in height and filled with water at 32 ± 1 °C. The control and metrnl groups remained sedentary during the experiments.

Metrnl Infusion

When the animals in the exercise group completed the swimming adaptation period and started swimming exercise, the i.p. injections of the control and metrnl groups were started. Rats in the metrnl group received i.p. a dose of 1µg/day of metrnl (CSB-EP719323RA, CusaBio, Wuhan, China) at 13:00-14:00 for about 19 consecutive days. Metrnl was dissolved in deionized water and administered to each rat in a volume of 1 mL/kg. The control group received a daily i.p. injection of 1 mL/kg deionized water in a similar manner.

Sample Processing

From the sixteenth day of injections of deionized water/metrnl and exercise training until the nineteenth day, the animals were sacrificed by decapitation at the estrous stage without anesthesia, to collect trunk blood and heart tissue samples. The blood samples were centrifuged at 4,500 rpm for 5 min at 4 °C to extract the serum. The serum samples were then kept at – 80 °C until the day when enzyme-linked immunosorbent assay (ELISA) was done. For histological examinations, the heart tissues excised from all groups were fixed in a 10% formalin.

Measurement of Musclin

The serum musclin levels were measured using a commercial rat-specific ELISA kit from SunRed Biotechnology Company (Cat no: 201-11-4519, Shanghai, China), following the manufacturer's instructions. The ELISA plate was measured at 450 nm using the ELISA plate reader (Multiskan FC, Thermo Scientific, USA). As reported by the manufacturer, the assay sensitivity was 0.55 ng/mL and the assay range was 0.8-125 ng/mL for the musclin ELISA.

Histology Studies

After fixation, the heart tissues were routinely processed and embedded in paraffin. For routine histological examination, serial 5-µm-thick sections at 30-µm intervals were prepared on microscope slides from all of the experimental groups tissue blocks. The sections of heart tissues were stained with hematoxylin-eosin for general histomorphologic analysis. For histochemical determination of mast cells and plasma cells, 5 µm sections from these blocks were stained with toluidine blue and methyl green-pyronin, respectively. All the preparations were studied and photographed with an examination microscope (Nikon Eclipse 50i).

Sections of heart tissue were stained with toluidine blue (0.5%, pH:0.5; Sigma-Aldrich, CAS 92-31-9) for ten minutes in order to evaluate mast cell count.[19] To ascertain the mast cell's numerical distribution in the tissue samples, ten areas of the heart tissue sections in all the experimental groups were chosen randomly and the mast cells were counted in each area, after which the results' arithmetic mean was calculated. This was done by counting mast cells using a 100-square ocular micrometer (eyepiece graticule) at a 40x magnification. All of the data was then converted into mast cell numbers inside a 1 mm^2 unit area.[20] This method was also used to determine the numerical distribution of plasma cells in 5-µm-thick heart sections stained with methyl green-pyronin (Histomed, BS-366, Lot: 102023.018) for 1.5 min.[21]

Statistical Analysis

Data was presented as mean ± standard error of the mean (SEM). Following the Shapiro-Wilk test to confirm the data's normality, the one-way analysis of variance (ANOVA), followed by Tukey's *post-hoc* test, was used to evaluate all of the data. The differences were considered statistically significant when P-value was < 0.05. The SPSS version 22.0 (IBM, Armonk, NY, USA) was used to perform the statistical analysis.

Results

The effects of exercise and metrnl on the histological changes in the heart tissues were analyzed by hematoxylin-eosin staining. Accordingly, as in the control group, normal cardiac histomorphology, including regular myocardial muscle fibers, intercalated discs and collateral connections was observed, in the exercise and metrnl groups. Nuclei were noted, centrally placed in myocytes and stained euchromatically (Figure 1).

As a result of examining the toluidine blue-stained heart tissue sections of each experimental group, mast cells in cardiac tissue were distinguished by their apparent metachromasia and determined to be round, oval or spindle-shaped in size. In most cells, centrally or eccentrically located nuclei were covered by granules. Mast cells were found to be located among the myocardial muscle fibers in cardiac tissue, chiefly in the epicardium and around the blood vessels (Figure 2A-C). As illustrated in Figure 2D, when compared to the control group, moderate-intensity exercise treatment significantly increased cardiac mast cell numbers in female rats (4.8 ± 0.4 and 7.89 ± 0.4, respectively, P < 0.001). In addition, the cardiac mast cell numbers showed a significant increase in the metrnl group, compared to the control rats (6.64 ± 0.5 and 4.8 ± 0.4, respectively, P = 0.025, Figure 2D).

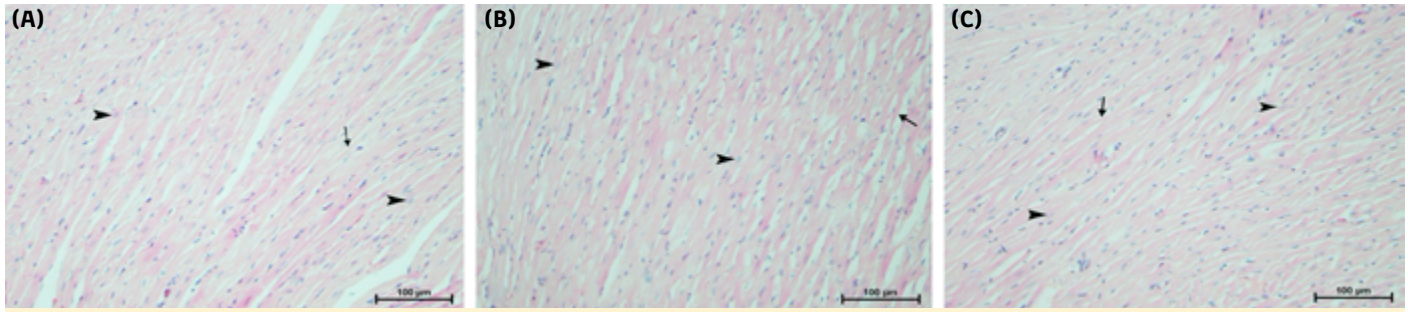

Figure 1. Histological slides of rat heart. (A) control group, (B) exercise group and (C) metrnl group (arrows indicating collateral connection and arrowheads indicating nucleus, hematoxylin and eosin stain, original magnification: 20x and scale bars: 100 µm).

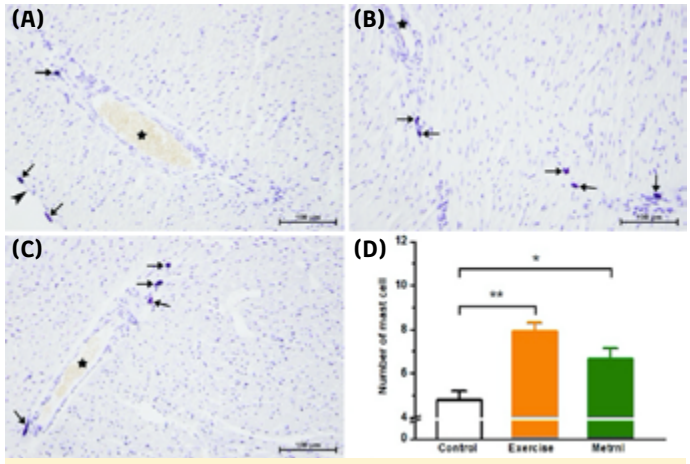

Figure 2. Effects of exercise or metrnl infusion on rat cardiac mast cells. Microscopic image of cardiac tissues in (A) control group, (B) exercise group and (C) metrnl group (arrows indicating mast cells, stars indicating blood vessels and arrowhead indicating pericardium, toluidine blue stain, original magnification: 20x and scale bars: 100 µm). (D) Mast cell counts (mean ± SEM), *P < 0.05, metrnl group vs. control group and **P < 0.001, exercise group vs. control group (one-way ANOVA followed by the Tukey's *post-hoc* test, n = 9 per group).

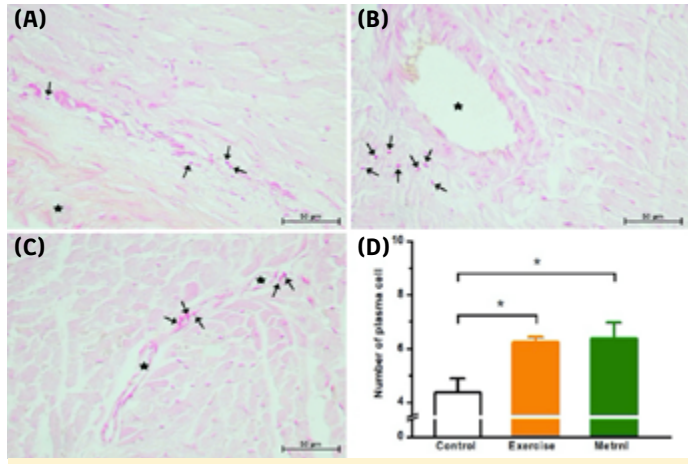

Figure 3. Effects of exercise or metrnl infusion on rat cardiac plasma cells. Microscopic image of cardiac tissues in (A) control group, (B) exercise group and (C) metrnl group (arrows indicating plasma cells and stars indicating blood vessels, methyl green-pyronin stain, original magnification: 40x and scale bars: 50 µm). (D) Plasma cell counts (mean ± SEM), *P < 0.05, metrnl or exercise groups vs. control group (one-way ANOVA followed by the Tukey's *post-hoc* test, n=9 per group).

In the heart tissues of all experimental groups, plasma cells stained with methyl green-pyronin were observed to be densely located in the epicardium and connective tissues around the blood vessels. It was determined that they were specifically found singly or in groups, around the blood vessels (Figure 3A-C). In the light microscopic examination, we found that plasma cell numbers in the heart tissues were significantly higher in the exercise group, in comparison to the control group (6.21 ± 0.2 and 4.37 ± 0.5, respectively, P = 0.049, Figure 3D). As in the exercise group, metrnl infusion significantly increased plasma cell numbers in the heart tissues of female rats (6.37 ± 0.6 vs. 4.37 ± 0.5 compared to the control group, P = 0.032, Figure 3D). Furthermore, the data obtained also revealed that the number of plasma cells, as well as mast cells, in the cardiac tissues of female rats were similar between the metrnl and exercise groups (Figure 2D and Figure 3D).

The concentrations of serum musclin in female rats in the estrous phase are presented in Figure 4. Compared to the control group, serum musclin levels were significantly decreased, depending on

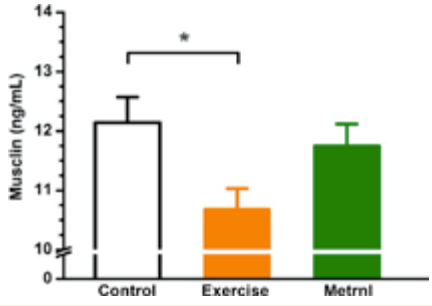

Figure 4. Effects of exercise or metrnl infusion on serum musclin levels in female rats. Data represent the mean ± SEM (n = 9 per group) *P < 0.05, exercise group vs. control group (one-way ANOVA followed by the Tukey's *post-hoc* test).

moderate-intensity exercise treatment in female rats (12.14 ± 0.43 ng/mL and 10.68 ± 0.35 ng/mL, respectively, P = 0.038). However, metrnl infusion did not affect the serum musclin levels in female rats (11.75 ± 0.37 ng/mL vs. 12.14 ± 0.43 ng/mL

compared to the control group, P > 0.05). Additionally, there was no significant difference in the serum musclin levels between the metrnl and exercise groups.

Discussion

In this study, we investigated the effects of metrnl, as an exercise-induced myokine, on mast cell and plasma cell numbers in the cardiac tissues of female rats, compared with moderate-intensity exercise. We also examined the changes in levels of the exercise-responsive myokine musclin during the effects of exercise and metrnl on the immune system cells. It was determined that metrnl increased mast cell and plasma cell numbers in the heart tissues like moderate-intensity exercise, but the rise in mast cell numbers was greater in female rats following moderate-intensity exercise. Additionally, serum musclin concentration in female rats was shown to decrease following moderate-intensity exercise and did not change with metrnl infusion. Accordingly, this study reported for the first time that exercise-induced metrnl may have a role in the immunoregulatory effects of moderate-intensity exercise in cardiac tissue, via immune cells.

The immune system is an intricate network of cells and molecules and it is affected by certain elements such as physiological factors, nutrition, environmental influences and exercise. Exercise causes physiological changes in the immune system by leading to changes in the number and function of immune cells.[1,22] However, the positive and negative effects of exercise on the immune system vary depending on the exercise variables, including intensity, duration and type of exercise. It has been stated that moderate-intensity exercise is beneficial for the immune system via stimulating cellular immunity, while intense exercise can depress immunity by decreasing the number and activity of immune system cells, in healthy humans.[23,24] For example, several studies have shown that moderate exercise caused greater increases in circulating immune cell counts, such as T and NK cells, than high-intensity exercise, and moderate-intensity exercise leads to stimulation of B cells.[25,26] In another study, it was shown that exercise-induced cardioprotection was associated with increased cardiac myeloid-derived suppressor cells in mice, modelled with isoproterenol-induced heart failure.[27] Consistent with these findings, in the present study we observed that moderate-intensity exercise may have an effect on immunity, by causing an increase in cardiac mast cells and plasma cells of female rats.

Metrnl, an exercise-inducible protein, plays a role in inflammatory responses and has been associated with innate and acquired immune functions and inflammatory pathways. Metrnl has been shown to have a role in innate immunity, based on its much higher expression in the heart, skin, colon, trachea, tongue and other mucosal sites.[28] In addition, the fact that metrnl can be generated by thymic medullary epithelial cells, suggests that metrnl may impact T-cell development and thus, immune function.[29] The role of metrnl in the immune system is also consistent with previous reports showing that metrnl induces increased M2 macrophage polarization in adipose tissue, an increase in adipose tissue eosinophils and increased immune cell recruitment to injured skeletal muscle.[30] Consistently, our results showed that exercise-induced metrnl increased the numbers of mast cells and plasma cells in the heart tissues of female rats, just like moderate-intensity exercise treatment.

Moderate-intensity exercise decreased the risk for cardiovascular disease by altering immune cell function.[31] Phungphong et al.[32] in 2016 demonstrated that increased cardiac mast cell degranulation in the ovariectomized rat heart, was decreased with moderate-intensity exercise. Thus, they stated that one of exercise's cardioprotective mechanisms is through modulation of cardiac mast cell activation. Furthermore, recent studies have reported that metrnl, a myokine, adipokine and cardiokine, has potential cardioprotective effects in helping cardiac hypertrophy, dysfunction, postinfarction recovery and myocardial ischemia/reperfusion injury.[13,33] However, current studies indicate that the underlying mechanism of metrnl in the cardioprotective effects remains unclear.[34]

Mast cells, multifunctional effector cells of the immune system, are localized in various regions of the heart tissue, including the myocardium (i.e., coronary artery wall and aortic valves), endocardium and epicardium. Recent studies have revealed that mast cells in these different locations may contribute to both physiological and pathological processes. At present, it has been stated that myocardial mast cells may potentially exhibit cardioprotective effects by contributing to the prevention and recovery of ischemic damage to the myocardium.[35,36] Studies have highlighted the potential benefits of bone marrow-derived B cells in improving cardiac function, after acute myocardial infarction. Similarly, Goodchild et al. in 2009 suggested that cardiac function was preserved by intramyocardial B cell injection into the early post-ischemic myocardium.[37,38] Likewise, the present study revealed that plasma cells, which represent the final stage of differentiation for all antigen-activated B cells and mast cells, may have a central role in the cardiac immune responses of metrnl and exercise. Consequently, we speculated that metrnl may have a function in the moderate-intensity exercise-induced improvements in cardiac immune response, by altering cardiac mast cell and plasma cell dynamics. These new findings suggest that metrnl may have important clinical implications for cardiovascular health.

Skeletal muscle produces the peptide known as musclin, an exercise-stimulated myokine, in response to exercise, and musclin levels vary with exercise intervention. Studies have shown that musclin levels in the systemic circulation increase in mice due to treadmill exercise and similarly, the treadmill-based endurance exercise training increased the circulating concentration of musclin in humans. In contrast, it has been reported that swimming intervention reduces musclin expression in skeletal muscle in rats.[14,39] Consistent with these findings, we observed that musclin levels decreased due to moderate-intensity swimming exercise in female rats. Additionally, for the first time in the literature, we report that exogenous metrnl infusion did not affect the musclin levels in female rats.

Regular, moderate-intensity exercise is linked with decreased circulating inflammatory cytokine levels, increased T-cell proliferation, greater natural killer cell cytotoxic activity and increased IL-2 production. All of these changes have been shown to indicate that regular, moderate-intensity exercise may improve or protect immunity.[24] Likewise, the current study determined that moderate-intensity exercise decreased the levels of the exercise-responsive myokine/cytokine musclin,

while increasing the number of cardiac mast cells, in female rats. Accordingly, this balance between the musclin levels and the number of mast cells due to moderate-intensity exercise, may be central in maintaining or improving immunity. In addition, the results of this study suggest that musclin may also be a candidate inflammatory cytokine in the cardiac immune response. Clinical implications of this study suggest that musclin level is a useful marker in the exercise-induced immune response.

Limitation of the Study

One potential limitation of our study is that it did not use immunohistochemical methods to identify mast cells and plasma cells in the cardiac tissue.

Conclusion

In conclusion, for the first time, our results show that metrnl increased mast cell and plasma cell numbers in cardiac tissue in female rats, like moderate-intensity exercise, but exercise intervention induced a greater increase in mast cell numbers and decreased musclin levels. Thus, it is suggested that the mechanisms underlying the modulation of the cardiac immune response of moderate-intensity exercise, are probably the effects of the exercise-responsive metrnl and musclin.

Ethics Committee Approval: Ethics committee approval was obtained from Animal Experimental Ethics Committee of Fırat University (Approval Number: 2023/16-06, Date: 20.09.2023).

Informed Consent: Written informed consent was not required for this study.

Conflict of Interest: The authors have no conflicts of interest to declare.

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The HALP Score's Prognostic Value for the Elderly Patients (≥ 75 years) Patients Following Percutaneous Coronary Intervention for Acute Myocardial Infarction

Akut Miyokard Enfarktüsü Nedeniyle Perkütan Koroner Girişim Uygulanan Yaşlı (≥ 75 yaş) Hastalarda HALP Skorunun Prognostik Değeri

ABSTRACT

Objective: Despite the reality that percutaneous coronary intervention (PCI) lowers mortality following acute myocardial infarction (AMI), older patients (≥ 75 years) are still at high risk of mortality. The purpose of this study was to evaluate the prognostic significance of the HALP score, which reflects the inflammatory and nutritional status, in this population.

Method: We retrospectively included 128 elderly patients who underwent PCI at our institution, between 2019 and 2022. The primary endpoint of the study was long-term, all-cause mortality. The study population was categorized into two distinct groups based on survival status: survivors and non-survivors. A multivariable Cox regression analysis was conducted to identify independent predictors of long-term all-cause mortality.

Results: The median follow-up time was 49.9 (35.6–62.74) months. In multivariable analysis, the HALP score and CRP independently predicted all-cause mortality at long-term follow-up (hazard ratio (HR): 0.96, 95% confidence interval (CI): 0.94–0.99, P = 0.003; HR: 1.04, 95% CI: 1.01–1.07, P = 0.020; respectively). Receiver operating characteristic curve analysis identified 26.252 as the optimal HALP score cut-off for predicting mortality (area under the curve (AUC): 0.764; 95% CI: 0.672–0.855; P < 0.001), with 73% sensitivity and 70.3% specificity. The HALP score demonstrated a higher AUC value, indicating better discriminative power compared to its individual components. In Kaplan–Meier analysis, patients with HALP score< 26.252 had a higher mortality during follow-up (log rank P < 0.0001).

Conclusion: The HALP score is an independent predictor of long-term all-cause mortality in older AMI patients following PCI.

Keywords: Coronary artery disease, elderly patient, HALP score, inflammation, malnutrition, mortality

ÖZET

Amaç: Perkütan koroner girişimin (PKG) akut miyokard infarktüsü (AMİ) sonrası mortaliteyi azaltmasına rağmen, yaşlı hastalar (≥75 yaş) hâlâ yüksek mortalite riski altındadır. Bu çalışmanın amacı, enflamatuvar ve beslenme durumunu yansıtan HALP skorunun bu popülasyondaki prognostik önemini değerlendirmektir.

Yöntem: 2019-2022 yılları arasında kurumumuzda PKG yapılan 128 yaşlı hastayı retrospektif olarak çalışmaya dâhil ettik. Çalışmanın birincil son noktası, uzun vadeli tüm nedenlere bağlı ölüm oranıydı. Çalışma popülasyonu, sağ kalım durumuna göre iki ayrı gruba ayrıldı: sağ kalanlar ve sağ kalamayanlar. Uzun vadeli tüm nedenlere bağlı mortalitenin bağımsız belirleyicilerini bulmak için çok değişkenli bir Cox regresyon modeli oluşturuldu.

Bulgular: Ortanca takip süresi 49,9 (35,6-62,74) aydı. Çok değişkenli analizde HALP skoru ve CRP, uzun dönem takipte tüm nedenlere bağlı mortaliteyi bağımsız olarak öngörmüştür (sırasıyla hazard ratio (HR): 0,96, %95 confidence interval (CI): 0,94-0,99, P = 0,003; HR: 1,04, %95 CI: 1,01-1,07, P = 0,020). Receiver operating characteristic (ROC) eğrisi analizi, 26,252 değerini %73 duyarlılık ve %70,3 özgüllük ile mortaliteyi öngörmek için en uygun kesme değeri olarak belirlemiştir (eğri altındaki alan (AUC): 0,764; %95 CI: 0,672-0,855, P < 0,001). ROC analizinde HALP skoru, daha yüksek bir AUC değeri göstererek kendi bileşenlerine kıyasla daha iyi ayırt edici güce sahip olduğunu ortaya koydu. Kaplan-Meier analizinde, HALP skoru <26,252 olan hastalarda takipte ölüm oranı daha yüksekti (log-rank P < 0,0001).

Sonuç: HALP skoru, yaşlı AMİ hastalarında PKG sonrası uzun dönem tüm nedenlere bağlı ölümün bağımsız bir öngördürücüsüdür.

Anahtar Kelimeler: Koroner arter hastalığı, yaşlı hasta, HALP skoru, inflamasyon, mortalite, malnütrisyon

ORIGINAL ARTICLE
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As the quality and accessibility of healthcare continue to improve worldwide, life expectancy is increasing. However, the prevalence of coronary artery disease (CAD) is likewise increasing as the population ages.[1] In older adults, CAD, particularly acute myocardial infarction (AMI), is a leading cause of morbidity and mortality. Elderly patients with AMI face a significantly higher risk of complications before, during, and after percutaneous coronary intervention (PCI) compared to younger populations. Their frailty, polypharmacy, reduced medication adherence, impaired renal function, increased stroke risk and dementia, negatively impacts their prognosis, leading to a higher mortality risk. Therefore, identifying prognostic markers to predict mortality in elderly patients undergoing PCI is crucial for improving patient management. Although some biomarkers have been associated with poor outcomes in AMI patients, specific markers that can reliably predict prognosis in high-risk elderly patients are still needed.

One of the main processes behind the development of atherosclerosis is inflammation.[2] Additionally, malnutrition is a fundamental indicator of frailty in elderly patients and serves as a predictor of worse outcomes in individuals with cardiovascular disease.[3] A new measure called the HALP score uses hemoglobin (Hb), lymphocyte (Lym), platelet (Plt), and albumin levels to assess a patient's nutritional and inflammatory conditions. Initially, the HALP score's potential predictive significance was examined in cancer patients.[4–6] Recent studies have demonstrated its prognostic significance in CAD, heart failure, and pulmonary thromboembolism.[7–13] Nevertheless, no prior assessment has been conducted on its prognostic importance, particularly in older individuals suffering from AMI. Thus, our goal was to find out how useful the HALP score was for predicting outcomes in older AMI patients undergoing PCI.

Materials and Methods

Study Design and Population

In this retrospective study, 1,863 consecutive patients who underwent PCI for AMI (including ST-elevation myocardial infarction (STEMI) and non-STEMI) at our hospital, between January 2019 and December 2022, were initially screened. Patients aged 75 years and older with technically successful procedures were examined. Based on the 2023 European Society of Cardiology Guidelines for the treatment of acute coronary syndromes, AMI diagnostic criteria were established.[14] Exclusion criteria were as follows: history of coronary artery bypass graft surgery, presentation with Killip class 4, failed PCI, hematologic and rheumatologic diseases, malignancy, insufficient or lost follow-up data, severe infection prior to admission, advanced hepatic or renal disease (glomerular filtration rate (GFR) < 15 mL/min/1.73 m^2 or receiving hemodialysis), including nephrotic syndrome, a history of blood transfusion prior to admission and in-hospital mortality. Ethics committee approval was obtained from Yalova University Health Sciences Non-Interventional Clinical Research Ethics Committee (Approval Number: 2025/81, Date: 05.02.2025), and the study was conducted in accordance with the Declaration of Helsinki's tenets. The study's retrospective methodology and the use of de-identified medical record data eliminated the need to obtain participants' formal informed consent.

ABBREVIATIONS

AMI	Acute myocardial infarction
AUC	Area under the curve
CAD	Coronary artery disease
CKD	Chronic kidney disease
CRP	C-reactive protein
DM	Diabetes mellitus
GFR	Glomerular filtration rate
Hb	Hemoglobin
HR	Hazard ratios
IQR	Interquartile range
Lym	Lymphocyte
MACE	Major adverse cardiac events
PCI	Percutaneous coronary interventions
Plt	Platelet
ROC	Receiver operating characteristic
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in myocardial ınfarction

Data Collection and Measurement of the HALP Score

The demographic and clinical data of the patients, along with laboratory results such as complete blood count and blood biochemistry, were obtained from the hospital database and electronic health records. Prior to the PCI surgery, blood samples were obtained from the antecubital vein and recorded in the medical records. Biochemical measurements were performed using a molecular analysis device (Roche Diagnostics, Mannheim, Germany). The following formula, which takes into account the levels of Hb, Lym, Plt and serum albumin, was used to determine the HALP score: Lym count (109/L) × albumin (g/L) × Hb (g/L)/Plt count (109/L).[15]

Outcomes and Definitions

At long-term follow-up (> 30 days following the index procedure), all-cause death was the main outcome; all-cause mortality refers to death resulting from any cause.[16] The date of death was obtained from the Provincial Health Directorate's Public Health Department, but the inability to determine the specific causes of death limited our ability to assess secondary endpoints. This represents one of the main limitations of our study.

The Thrombolysis in Myocardial Infarction (TIMI) criteria were used to categorize antegrade coronary flow following PCI (TIMI 0: no antegrade flow, TIMI I: penetration without perfusion, TIMI II: partial perfusion and TIMI III: full perfusion).[17] Pre-procedural TIMI flow was defined as pre-TIMI flow.[18] Technical success was characterized by achieving TIMI grade 3 flow in the target vessel with residual stenosis below 30%, whereas failure to meet these criteria was defined as failed PCI.[19]

In the present study, the thrombus burden assessed via coronary angiography was stratified into six categories. Grade 0 represented the absence of angiographic thrombus. Grade 1 indicated a possible presence of thrombus, suggested by findings such as decreased contrast density, haziness or an irregular lesion contour. Grade 2 was defined as a definite thrombus with its largest dimension measuring less than 50% of the vessel's

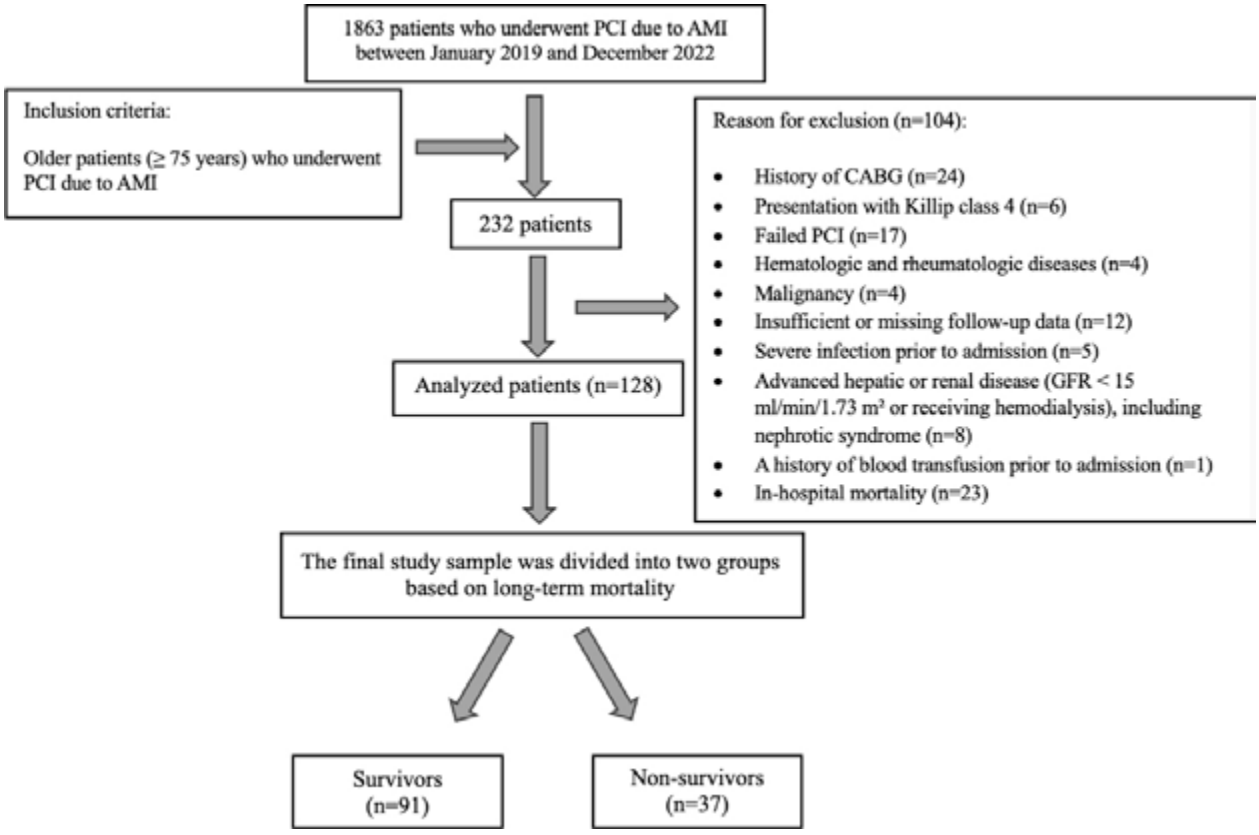

Figure 1. Flowchart of study population.

AMI, Acute myocardial infarction; CABG, Coronary artery by-pass grafting; PCI, Percutaneous coronary interventions; GFR, Glomerular filtration rate.

diameter. Grade 3 included thrombi whose largest dimension exceeded 50% but remained below two vessel diameters. Grade 4 referred to thrombi measuring more than two vessel diameters in size. Lastly, Grade 5 represented a thrombus causing complete occlusion of the affected vessel.[20] Following the restoration of antegrade flow using a guidewire or balloon dilatation, grade 5 angiographic thrombus load was reclassified. Based on the final thrombus burden, patients with grade 1–3 thrombus load were classified as having a moderate thrombus burden, whereas those with grade 4–5 thrombus burden were classified as having a severe thrombus burden.[20,21]

Statistical Analysis

The Jamovi version 2.6.2 (The Jamovi project, Sydney, Australia) with the "ggplot," "Hmisc," and "rms" packages were used for all statistical methods. Depending on the distribution, continuous variables were presented as median and interquartile range (IQR) or mean and standard deviation. The Kolmogorov-Smirnov test was employed to determine normalcy. Counts and percentages were used to display categorical variables. The Mann-Whitney U test and the independent samples t-test were used to compare independent continuous variables, while Fisher's exact test or Pearson's chi-squared test were used to analyze categorical data. To find independent predictors of mortality, a multivariable Cox regression analysis was used. Clinical relevance served as the foundation for the development of statistical models. Hazard ratios (HR) and 95% confidence intervals (CI) were used to express the findings. The predictive power of the HALP score, Hb, Lym count and albumin levels for mortality was evaluated using the area under the curve (AUC) values, obtained from receiver operating characteristic (ROC) analysis. The Kaplan–Meier technique was used to examine survival times after the follow-up period. From the date of diagnosis until the date of death or final follow-up, the overall survival was computed. Using the log-rank test, group differences were evaluated. For all analyses, a p-value of less than 0.05 was deemed statistically significant.

Results

The median follow-up duration was 49.9 (35.6–62.74) months in this study. A total of 23 patients experienced in-hospital mortality. After applying the inclusion and exclusion criteria, the final analysis included 128 patients over the age of 75 who underwent PCI with technical success (Figure 1). Of these, 76 (59%) were male and the median age was 79 (77–83). Two groups were created from the research population according to their mortality status: 37 patients (29%) were in the non-survivor group, while 91 patients (71%) were in the survivor group. Table 1 displays the research population's demographics and clinical results. Patients' median length of stay in the hospital was three (3–4) days. The female gender was more prevalent in the non-survivor group, and both the mean age and length of hospital stay were higher in this group (P <0.05 for all).

Table 1. Baseline characteristics of the study population according to mortality status

Variables	All patients (n = 128)	Survivors (n = 91, 71%)	Non-survivors (n = 37, 29%)	P
Demographic features and risk factors				
Gender (male), n (%)	76 (59)	59 (65)	17 (46)	**0.049**
Age (years)	79 (77–83)	78 (76–82)	81 (79–85)	**0.002**
DM, n (%)	47 (37)	33 (36)	14 (38)	0.867
HT, n (%)	63 (49)	42 (46)	21 (57)	0.277
HL, n (%)	29 (23)	18 (20)	11 (30)	0.248
PCI history, n (%)	26 (20)	18 (20)	8 (22)	0.814
CKD, n (%)	61 (48)	39 (43)	22 (59)	0.088
CVD, n (%)	5 (4)	3 (3)	2 (5)	0.577
AF	13 (10)	9 (10)	4 (11)	0.876
EF (%)	55 (48–60)	55 (45–60)	55 (50–60)	0.663
CA-AKI	23 (18)	16 (18)	7 (19)	0.858
Smoking, n (%)	11 (9)	10 (11)	1 (3)	0.129
STEMI/non-STEMI, n (%)	74 (59)	50 (57)	24 (65)	0.403
Length of hospital stay (day)	3 (3-4)	3 (3-4)	3 (3-5)	**0.049**
Follow-up time (month)	49.88 (35.6–62.74)	54.17 (42.37–66.6)	33 (10.83–48.73)	**<0.001**

The data are presented as percentages and median (interquartile range). Statistical significance was defined as P < 0.05 and indicated in bold. AF, Atrial fibrillation; CA-AKI, Contrast-associated acute kidney injury; CKD, Chronic kidney disease; CVD, Cerebrovascular disease; DM, Diabetes mellitus; EF, Ejection fraction; HL, Hyperlipidemia; HT, Hypertension; PCI, Percutaneous coronary intervention; STEMI, ST Elevation myocardial infarction.

Table 2 displays the research population's laboratory results. The non-survivor group had considerably lower levels of Hb, albumin, Lym counts, and HALP score than the survivors group (P <0.001, and P <0.001, respectively). On the other hand, the non-survivor group's C-reactive protein (CRP) levels were substantially greater than those of the survivors group (P <0.001). A comparison of HALP scores between the survivor and non-survivor groups using a box plot is shown in Figure 2. Periprocedural features of PCI in the study population were comparable between the groups (Table 3).

A multivariable Cox proportional hazards regression model was constructed to identify potential factors associated with all-cause mortality. The development of the model was guided by clinical relevance and variables that may influence mortality, including age, sex, diabetes mellitus (DM), chronic kidney disease (CKD), ejection fraction, CRP and the HALP score, were included in the model. In this model, the HALP score and CRP independently predicted all-cause mortality at long-term follow-up (HR: 0.96, 95% CI: 0.94–0.99, P = 0.003; HR: 1.04, 95% CI: 1.01–1.07, P = 0.020; respectively). Figure 3 depicts a forest plot for multivariable analysis showing variables linked to all-cause mortality. In addition, Figure 4 illustrates the estimated effect of HALP score on the HR for mortality based on a multivariable Cox proportional hazards model. A lower HALP score is associated with a higher risk of mortality, suggesting that HALP may serve as an independent prognostic marker (Table 4).

According to the ROC curve analysis, the ideal cut-off value of the HALP score for forecasting all-cause death was 26.252 (Figure 5). At this threshold, the AUC was 0.764 (95% CI: 0.672–0.855; P <0.001), with a sensitivity of 73% and a specificity of 70.3%. The HALP score demonstrated a higher AUC value, indicating better discriminative power compared to each of its individual components (Hb, albumin, Plt and Lym count).

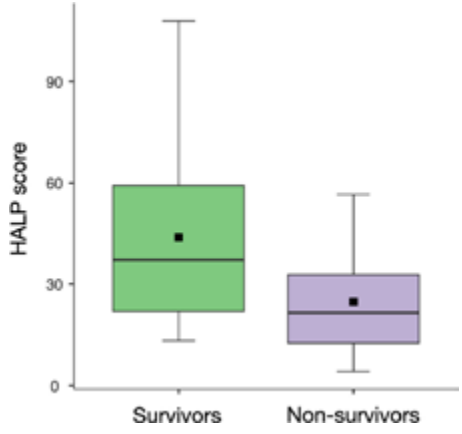

Figure 2. Comparison of HALP scores between the survivors and non-survivors group using a box plot.

A single-arm Kaplan–Meier analysis revealed that the overall 60-month survival rate after PCI in elderly patients was 69.1%. (Figure 6A). The cumulative all-cause mortality rates at 1, 3 and 5 years were 8.6% (n = 11), 15.8% (n = 20), and 30.9% (n = 33), respectively. When stratified by the HALP score cut-off value derived from the ROC analysis, patients with a low HALP score (47.2%) had a considerably lower 60-month survival rate than those with a high HALP score (85.9%) (log-rank test, P < 0.0001) (Figure 6B).

Table 2. Baseline laboratory findings of the study population according to mortality status

Variables	All patients (n = 128)	Survivors (n = 91, 71%)	Non-survivors (n = 37, 29%)	P
HbA1c (%), n (%)	5.9 (5.5–6.7)	5.8 (5.5–6.65)	6.15 (5.7–6.85)	0.182
Urea (mg/dL)	43 (34–50.15)	42.9 (34–48.9)	45 (33.95–52.25)	0.533
Creatinine (mg/dL)	1.08 (0.88–1.33)	1.08 (0.86–1.3)	1.01 (0.90–1.35)	0.584
GFR	59.1 ± 17.4	59.81 ± 16.29	57.3 ± 20.1	0.484
Sodium (mEq/L)	139 (137–140)	139 (137–140)	139 (138–140)	0.681
Potassium (mmol/L)	4.25 (4.07–4.6)	4.23 (4.0–4.5)	4.26 (4.1–4.7)	0.827
Total-C (mg/dL)	189.6 ± 41.5	190.5 ± 40.33	187.35 ± 44.77	0.698
HDL-C (mg/dL)	43 (38.5–51)	42.5 (37.25–50)	44 (40–53)	0.344
TG (mg/dL)	120 (92–167)	123.5 (95–191)	110 (84–140)	0.096
LDL-C (mg/dL)	120.72 ± 33.3	121.09 ± 31.27	119.8 ± 38.2	0.845
CRP (mg/L)	2 (0.84–4)	2 (0.5–3)	4 (3–7.40)	**<0.001**
Albumin (g/L)	4 (3.7–4.1)	4 (3.8–4.1)	3.9 (3.6–4)	**0.046**
Peak troponin	13.4 (4–25)	16 (5.15–25)	9.30 (2.5–25)	0.222
WBC (10^3/μL)	9.7 ± 3.2	9.75 ± 3.18	9.56 ± 3.25	0.757
Neu (10^3/μL)	6.75 (4.7–9.3)	6.4 (4.29–8.7)	7.7 (5.3–9.7)	0.10
Lym (10^3/μL)	1.6 (1.1–2.14)	1.7 (1.29–2.30)	1.1 (0.97–1.60)	**<0.001**
Mon (10^3/μL)	0.55 (0.40–0.70)	0.60 (0.41–0.70)	0.50 (0.40–0.60)	0.109
Hb (g/dL)	12.6 ± 1.8	12.87 ± 1.68	12.06 ± 1.95	**0.020**
Plt (10^3/μL)	241 (198.7–306.2)	239 (198–280)	243 (200–357)	0.140
Glucose	118.5 (101–157)	117 (99.5–146)	137 (107–180)	0.064
AST	20 (16.65–31)	20 (16.07–28)	22 (17–40)	0.251
ALT	15 (12–21)	15 (12–20.75)	15 (11–21)	0.949
HALP score	30.76 (19.97–50)	37.09 (22–59.2)	22 (12.53–28.1)	**<0.001**

The data are presented as percentages, mean ± standard deviation, or median (interquartile range). Statistical significance was defined as P < 0.05 and indicated in bold. ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C reactive protein; GFR, Glomerular filtration rate; Hb, Hemoglobin; HbA1c, Glycated hemoglobin; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein; Lym, Lymphocyte; Mon, Monocyte; Neu, Neutrophil; Plt, Platelet; TG, Triglyceride; Total-C, Total cholesterol; WBC, White blood cell.

Discussion

The predictive importance of the HALP score in elderly AMI patients undergoing PCI was examined in this investigation. According to our research, the HALP score and CRP are both reliable indicators of long-term mortality following PCI. The HALP score has the potential to be a useful tool for risk stratification in this patient group, as evidenced by the fact that patients with low scores had much greater mortality rates during long-term follow-up than patients with high scores. This is the only study that we are aware of that shows the HALP score has prognostic significance for long-term all-cause mortality in elderly (≥ 75 years) AMI patients after PCI.

Due to population aging, the number of patients over 75 is continuously rising and CAD, particularly AMI, continues to be the leading cause of mortality among elderly patients. These patients undergoing PCI had a much higher risk of major adverse cardiac events (MACE) and death both in-hospital and during follow-up.[22] It has been demonstrated that older patients have more complicated lesions, left main lesions and severe coronary disease; as a result, they constitute a group with greater risk features.[23] However, this increased risk should not imply that PCI should be avoided in elderly patients. The decision to perform PCI should be individualized, and identifying high-risk patients during long-term follow-up may help improve clinical outcomes. To enable the early identification of older individuals at greater risk of death, a straightforward and easily accessible risk score is therefore required.

A novel metric derived from basic laboratory data is the HALP score, which represents the nutritional and systemic inflammatory condition of patients.[24] Each one of the score's components is essential to determining a patient's overall health.[25] Anemia and malnutrition are indicated by lower Hb and albumin levels, while inflammation and a compromised immune system are associated with elevated Plt and decreased Lym counts.[10] The HALP score's predictive power was first investigated in patients with gastric cancer.[26] Furthermore, in a meta-analysis including 13,038 cancer patients with solid tumors, a low HALP score was associated with decreased overall survival.[6] Current studies focus on the predictive value of the HALP score in cardiovascular diseases.[7–9,10–13,24,27] Karakayali et al.[10] showed that in patients with STEMI undergoing primary PCI, the HALP score was an independent predictor of in-hospital death. Similarly, Toprak et al.[12] found that the HALP score was a reliable indicator of short-term prognosis and

Table 3. Comparison of angiographic and periprocedural features of patients in the study population according to mortality status

Variables	All patients (n = 128)	Survivors (n = 91, 71%)	Non-survivors (n = 37, 29%)	P
Angiographic features				
Femoral vs radial access, n (%)	53 (41)	33 (36)	20 (54)	0.064
Culprit lesion, n (%)				0.337
LMCA	1 (1)	0 (0)	1 (3)	
LAD	49 (38)	37 (41)	12 (32)	
CX	28 (22)	19 (21)	9 (24)	
RCA	50 (39)	35 (38)	15 (41)	
Pre-TIMI flow, n (%)				0.591
0	64 (50)	49 (54)	15 (41)	
1	8 (6)	5 (5)	3 (8)	
2	21 (16)	14 (15)	7 (19)	
3	35 (27)	23 (25)	12 (32)	
Thrombus TIMI grade, n (%)				0.073
0	5 (4)	5 (5)	0 (0)	
1	24 (19)	20 (22)	4 (11)	
2	50 (39)	37 (41)	13 (35)	
3	30 (23)	18 (20)	12 (32)	
4	15 (12)	10 (11)	5 (14)	
5	4 (3)	1 (1)	3 (8)	
High grade thrombus	19 (15)	11 (12)	8 (22)	0.169
CTO	8 (6)	5 (5)	3 (8)	0.580
Coronary ectasia	22 (17)	16 (18)	6 (16)	0.853
Presence of severe lesion, n (%)				
LMCA	5 (4)	2 (2)	3 (8)	0.118
LAD	79 (62)	22 (59)	22 (59)	0.737
CX	45 (35)	29 (32)	16 (43)	0.222
RCA	69 (54)	46 (51)	23 (62)	0.232
Peri-procedural features				
No-reflow, n (%)	8 (6)	6 (7)	2 (5)	0.801
Amount of contrast media	204.1 ± 72.9	198.2 ± 66.6	218.6 ± 85.6	0.152

The data are presented as percentages, mean ± standard deviation. Statistical significance was defined as P < 0.05 and indicated in bold. CTO, Chronic total occlusion; CX, Circumflex artery; LAD, Left anterior descending artery; LMCA, Left main coronary artery; RCA, Right coronary artery; TIMI, Thrombolysis in myocardial infarction.

no-reflow in STEMI patients. The HALP score was associated with both no-reflow and long-term MACE in STEMI patients after primary PCI, according to Liu et al.[24] Furthermore, Kılıç et al.[27] showed that a low HALP score was associated with both in-hospital and one-year mortality in non-STEMI patients.

In this study, we found that the HALP score was an independent predictor of long-term mortality in older AMI patients after PCI. There are a number of reasons why a low HALP score is linked to long-term mortality. First off, the Hb, albumin, Lym and Plt counts that make up the HALP score are all significant biomarkers that affect prognosis in the elderly. Low Plt counts indicate systemic inflammation, low Lym numbers indicate immunological dysfunction, and anemia and hypoalbuminemia represent dietary inadequacy as well as general weakness. A decline in immunological and nutritional health may be indicated by the combination of these measures, which might have an adverse effect on cardiovascular healing processes. Furthermore, these characteristics are frequently linked to comorbid illnesses that might raise the risk of death, such as CKD, cancer or chronic inflammatory disorders. In order to predict long-term outcomes for older patients with AMI, a straightforward instrument like the HALP score—which is based on regular laboratory data—may be clinically useful.

Additionally, long-term mortality has been linked to increased CRP levels in several research publications in the literature. For instance, Kinjo et al.[28] discovered that in patients with AMI, CRP concentration was an independent predictor of long-term cardiovascular and all-cause mortality. Similarly, Xia et al.[29] reported

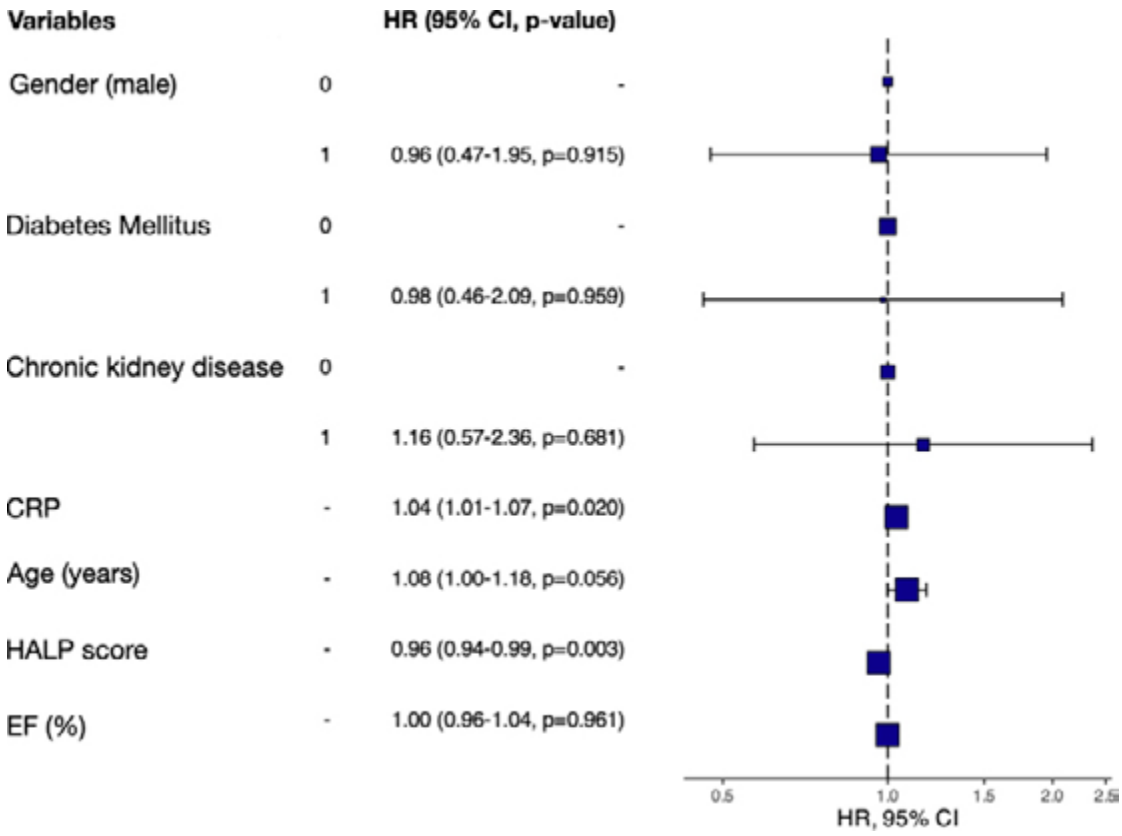

Figure 3. Predictors associated with all-cause mortality in elderly patients who underwent percutaneous coronary intervention.

HR, Hazard ratio; CI, Confidence interval; CRP, C-reactive protein; HALP, Hemoglobin, albumin, lymphocyte, and platelet; EF, Ejection fraction.

that CRP was an independent predictor of long-term all-cause, cardiovascular and cardiac mortality following AMI, regardless of DM status. Our research also shows that high CRP levels are an independent predictor of higher long-term mortality in older AMI patients, which is in line with previous findings. These findings emphasize the importance of systemic inflammation in predicting outcomes for patients with AMI and the potential use of CRP as a straightforward yet effective biomarker for risk assessment.

Our study concludes by highlighting the HALP score's potential as a helpful indicator of long-term mortality in older AMI patients after PCI. By closely monitoring this group, HALP score evaluation might be included in standard clinical practice to assist in identifying high-risk patients and enhance outcomes. The usefulness of the HALP score in forecasting morbidity and death in elderly AMI patients after PCI, however, requires more research with long-term follow-up.

Table 4. Multivariable logistic Cox regression analysis for prediction of mortality

	Multivariable Cox Regression Analysis	
Variables	**HR (95%, CI)**	**P**
Age (years)	1.08 (1.00–1.18)	0.056
Gender (male)	0.96 (0.47–1.95)	0.915
DM	0.98 (0.46–2.09)	0.959
CKD	1.16 (0.57–2.36)	0.681
EF	1.00 (0.96–1.04)	0.961
CRP (mg/L)	1.04 (1.01–1.07)	**0.020**
HALP score	0.96 (0.94–0.99)	**0.003**

Statistical significance was defined as P < 0.05 and indicated in bold. CKD, Chronic kidney disease; CRP, C-reactive protein; DM, Diabetes mellitus; EF, Ejection fraction.

Limitations

The association between HALP score and mortality in older patients who underwent PCI may be further supported by these findings. However, our study has a number of limitations. It was retrospective in design and based on data obtained from medical records, which may lead to selection and information bias. Despite the limited sample size, the study reflected a specific patient group. Due to the lack of access of the National Death Notification System database, the causes of death could not be determined. Therefore, we reported the primary endpoint as overall mortality and were unable to assess the secondary outcome. Furthermore, our study did not assess frailty, nor did it compare the HALP score to established cardiovascular risk assessment tools. Data regarding the rates of optimal medical therapy and specific drug usage among patients following acute myocardial infarction were also not available in this study. This limitation may affect the comprehensive assessment of determinants of long-term survival and should be considered when interpreting the results.

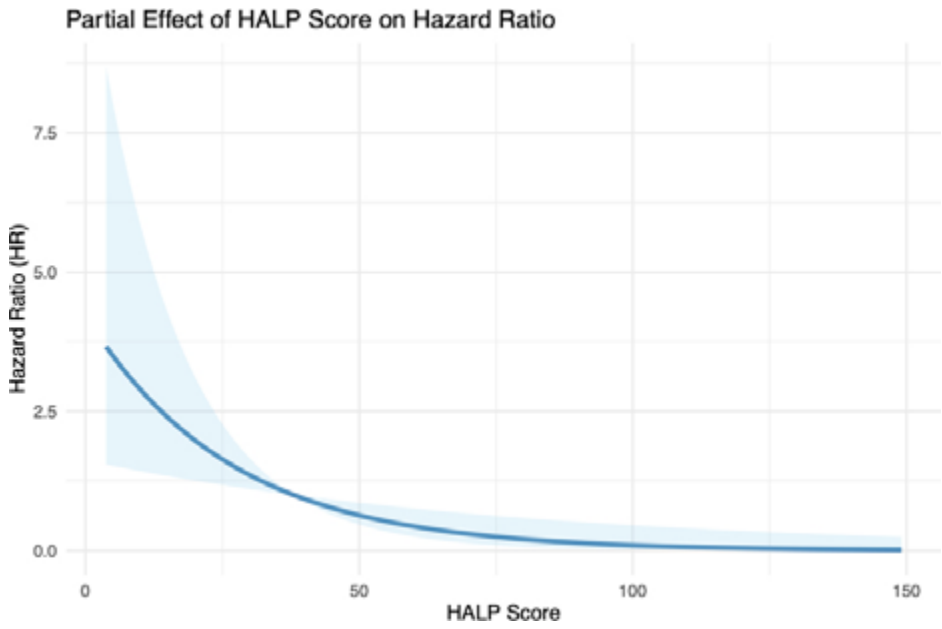

Figure 4. Partial effect plot of HALP score on hazard ratio for mortality. The plot illustrates the estimated effect of HALP score on the hazard ratio for mortality based on a multivariable Cox proportional hazards model. The blue line represents the predicted hazard ratio across the range of HALP scores, adjusted for age, gender, chronic kidney disease, CRP, ejection fraction, and diabetes mellitus. The shaded area indicates the 95% confidence interval.

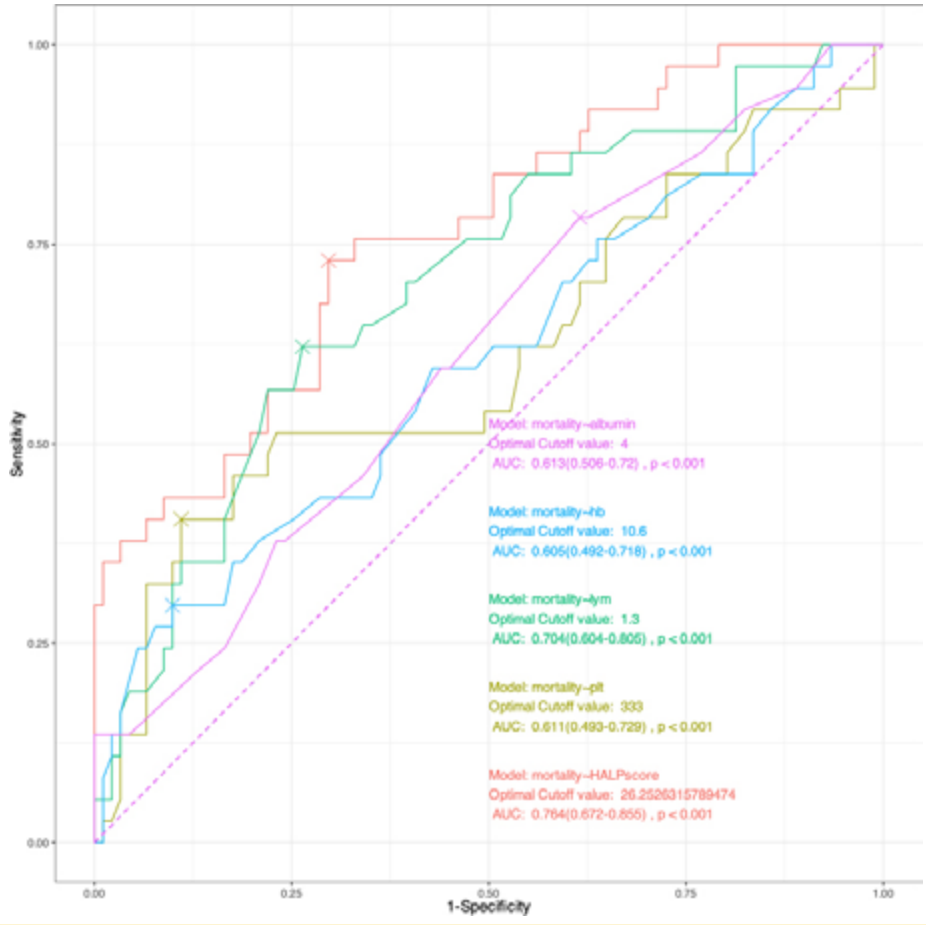

Figure 5. ROC curve analysis of the HALP score and its individual components in predicting mortality among elderly patients with acute myocardial infarction.

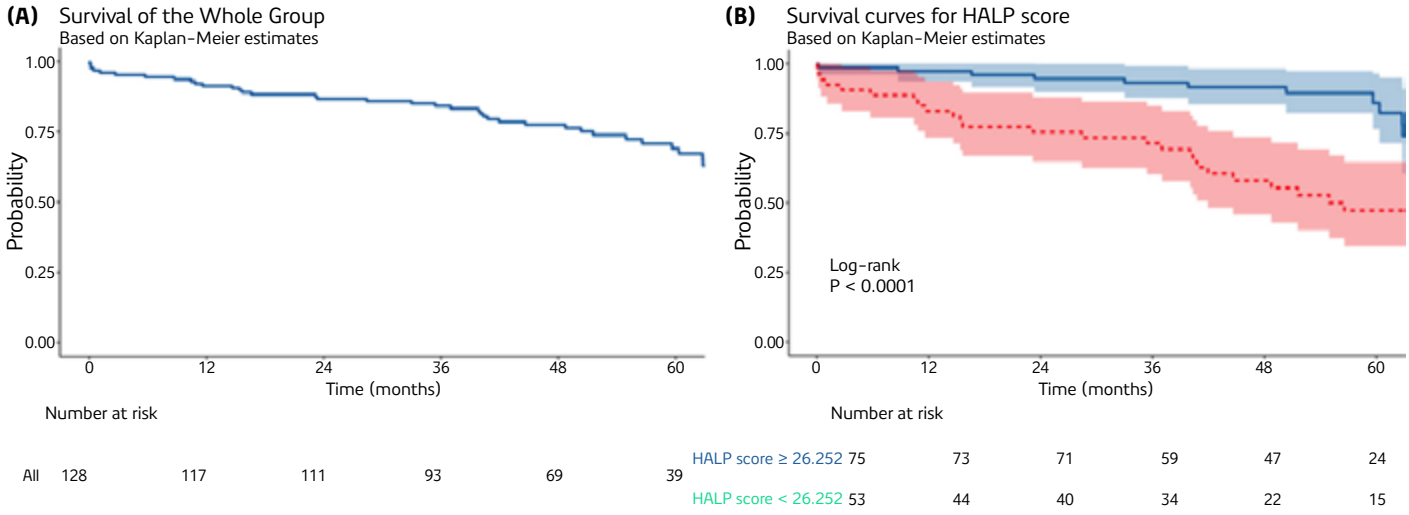

Figure 6. (A) A single-arm Kaplan–Meier analysis. (B) Kaplan–Meier survival curves for all-cause mortality, according to the HALP score.

Conclusion

Elderly patients represent a high-risk cohort with elevated long-term overall mortality rates. In this population, the HALP score may serve as a potential prognostic marker for survival. Despite their increased risk, revascularization should not be deferred solely due to age in these patients. The HALP score may be a valuable tool to support personalized clinical decision-making regarding PCI in elderly individuals.

Ethics Committee Approval: Ethics committee approval was obtained from Yalova University Health Sciences Non-Interventional Clinical Research Ethics Committee (Approval Number: 2025/81, Date: 05.02.2025).

Informed Consent: Informed consent was not required for this study, as approved by the institutional ethics committee, due to its retrospective design and use of de-identified patient data.

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Association Between Right Ventricular Echocardiographic Parameters and HFA-PEFF Score in Heart Failure with Preserved Ejection Fraction

Korunmuş Ejeksiyon Fraksiyonlu Kalp Yetersizliğinde Sağ Ventrikül Ekokardiyografik Parametreleri ile HFA-PEFF Skoru Arasındaki İlişki

ABSTRACT

Objective: Heart failure with preserved ejection fraction (HFpEF) is a leading clinical syndrome, accounting for more than 50% of hospitalizations due to heart failure. The Heart Failure Association Pre-test assessment, Echocardiography and natriuretic Peptides, Functional testing and Final etiological diagnosis (HFA-PEFF) algorithm, used for the diagnosis of HFpEF, also has prognostic value. The primary purpose of this work was to explore the relationship between the HFA-PEFF score and right ventricular (RV) echocardiographic parameters.

Method: 127 patients diagnosed with HFpEF between January 2021 and November 2024, with adequate transthoracic echocardiography (TTE) images, were retrospectively evaluated. Patients were categorized into three prognostic risk groups based on their HFA-PEFF scores: low (0–2), intermediate (3–4) and high (5–6). RV function was assessed using Tricuspid annular plane systolic excursion (TAPSE), tricuspid annular S' velocity and RV free wall longitudinal strain (RVFW GLS). The relationship between the HFA-PEFF score and RV parameters was evaluated using One-way ANOVA and Spearman correlation analysis.

Results: Patients with high HFA-PEFF scores showed significant deterioration in TAPSE and RV GLS values. A moderate negative correlation was observed between HFA-PEFF score and RVFW GLS ($r = 0.50$, $P < 0.001$), while a mild negative correlation was found with TAPSE ($r = -0.35$, $P < 0.001$).

Conclusion: In HFpEF patients with poor prognosis as identified by the HFA-PEFF score, there was a marked deterioration in RV parameters, particularly RVFW 2D GLS and TAPSE. These findings suggest that incorporating RV parameters into HFpEF diagnostic and prognostic algorithms might provide additional clinical value.

Keywords: Heart failure with preserved ejection fraction, HFA-PEFF score, right ventricular function

ÖZET

Amaç: Korunmuş ejeksiyon fraksiyonlu kalp yetersizliği (KEFKY), kalp yetersizliği nedeniyle hastaneye yatışların yüzde 50'sinden fazlasını oluşturan önemli bir klinik sendromdur. KEFKY tanı algoritması olarak belirlenen HFA-PEFF, aynı zamanda prognostik öneme sahiptir. Çalışmanın birincil amacı, HFA-PEFF skorunun sağ ventrikül (RV) eko parametreleri ile ilişkisini araştırmaktır.

Yöntem: Ocak 2021 - Kasım 2024 tarihleri arasında KEFKY tanısı almış, uygun transtorasik ekokardiyografi (TTE) görüntülerine sahip 127 hasta retrospektif olarak değerlendirildi. Hastalar, HFA-PEFF skoruna göre düşük (0–2), orta (3–4) ve yüksek (5–6) kötü prognostik risk gruplarına ayrıldı. RV fonksiyonları; TAPSE, triküspit anulus S velositesi ve RV serbest duvar longitudinal strain (RV GLS) parametreleri ile ölçüldü. HFA-PEFF skoru ile RV parametreleri arasındaki korelasyon Spearman istatistiksel metodu ile değerlendirildi.

Bulgular: Yüksek HFA-PEFF skoruna sahip hastalarda TAPSE ve RV GLS değerlerinde anlamlı bozulma görüldü. HFA-PEFF skoru ile RV GLS arasında orta düzeyde korelasyon ($r = -0,50$, $P < 0,001$); TAPSE ile ise hafif korelasyon ($r = -0,35$, $P < 0,001$) bulundu.

Sonuç: HFA-PEFF ile belirlenen kötü prognoz riskine sahip KEFKY hastalarında, sağ ventrikül parametrelerinden özellikle sağ ventrikül 2D longitudinal strain ve TAPSE'de belirgin bozulma olduğu gösterilmiş olup bu bulgular, KEFKY tanı ve prognoz algoritmalarında sağ ventrikül parametrelerinin de eklenmesinin ek katkı sağlayabileceğini düşündürmektedir.

Anahtar Kelimeler: Korunmuş ejeksiyon fraksiyonlu kalp yetmezliği, HFA-PEFF skoru, sağ ventrikül fonksiyonu

ORIGINAL ARTICLE
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Heart failure with preserved ejection fraction (HFpEF) has increasingly gained attention as a complex clinical syndrome, largely due to advances in research and the refinement of diagnostic criteria. Its prevalence is steadily rising and it is predicted that in the near future, it will surpass heart failure with reduced ejection fraction (HFrEF) in prevalence.[1,2]

Numerous parameters are used to diagnose HFpEF. However, due to the presence of various specific diseases under this umbrella term and the resulting broad clinical spectrum, a clear and unified diagnostic algorithm is lacking. The European Society of Cardiology (ESC) heart failure guidelines recommend using echocardiographic parameters and blood biomarkers alongside clinical findings, for diagnosis.[3] In 2019, the ESC Heart Failure group developed a diagnostic algorithm for HFpEF.[4] The Heart Failure Association Pre-test assessment, Echocardiography and natriuretic Peptides, Functional testing and Final etiological diagnosis (HFA-PEFF) diagnostic algorithm includes transthoracic echocardiographic (TTE) parameters, originally part of the 2016 ESC diastolic dysfunction guideline, to assess left ventricular (LV) filling pressures, along with other markers recommended in the ESC HFpEF diagnostic algorithm. LV global longitudinal strain (LV GLS) is also included as a minor criteria.[4] Subsequent trials have demonstrated that the HFA-PEFF score is associated with prognosis in patients with HFpEF.[5]

Contrary to common belief, HFpEF can affect the right ventricle (RV) even in its early stages and the presence of RV dysfunction in HFpEF is related to poor prognosis. However, apart from tricuspid regurgitation (TR) jet velocity, no other parameter reflecting RV dysfunction has been incorporated into diagnostic or prognostic algorithms, despite its significant clinical implications.[6,7] This study aimed to explore how right ventricular (RV) echocardiographic parameters relate to the HFA-PEFF algorithm, a tool with both diagnostic and prognostic relevance in HFpEF.

ABBREVIATIONS

AFI	Automated Function Imaging
ASE/EACVI	American Society of Echocardiography and the European Association of Cardiovascular Imaging
EF	Ejection fraction
ESC	European Society of Cardiology
GLS	Global longitudinal strain
HFA-PEFF	Heart Failure Association Pre-test assessment, Echocardiography and natriuretic Peptides, Functional testing and Final etiological diagnosis
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LAVI	Left atrial volume index
LV	Left ventricle
LV GLS	LV global longitudinal strain
ROI	Region of interest
RV	Right ventricle
TAPSE	Tricuspid annular plane systolic excursion
TAVI	Transcatheter aortic valve implantation
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiographic

Materials and Methods

Patient Inclusion and Exclusion Criteria

The study was conducted in accordance with the Declaration of Helsinki. This retrospective observational study was designed with the following inclusion and exclusion criteria:

Inclusion criteria: Patients diagnosed with HFpEF and admitted to our clinic between January 2021 and November 2024 were retrospectively evaluated. Patients over the age of eighteen with TTE images suitable for left and right ventricular measurements, as well as good quality for the assessment of global longitudinal strain (GLS), were included in the study.

Exclusion criteria: Reduced EF (EF < 50%), acute coronary syndromes, coronary artery bypass surgery, moderate-to-severe valvular disease, previous valve operations, pulmonary hypertension due to causes other than Group 2 (e.g., chronic lung disease, chronic thromboembolic pulmonary hypertension, pulmonary arterial hypertension, endocrine or connective tissue diseases), constrictive pericarditis, congenital heart diseases or renal failure (GFR < 60 ml/min), were excluded from the study. After obtaining ethical approval from the Ankara University Faculty of Medicine Human Research Ethics Committee (Approval Number: İ1-22-21, Date: 14.01.2021), echocardiographic images of 326 eligible patients were reviewed. Images were retrieved from the EchoPac archive system of the Ankara University Echocardiography Laboratory. A total of 127 patients with suitable images for left and right ventricular assessment were included in the study.

General Evaluation and Measurements

Hospital records were used to obtain the clinical and demographic characteristics of the 127 patients. Laboratory data from within 24–48 hours prior to the TTE were recorded. Cardiovascular risk factors and medications used by the patients were also extracted from the archives.

HFA-PEFF Score

The HFA-PEFF score was published in detail by the ESC Heart Failure Association in 2019 as a consensus report.[4] In essence, the score is based on three main components functional, morphological, and biomarker. Major criteria in each component score two points, while minor criteria score one point. However, each component can contribute a maximum of two points. If at least one major criteria is positive in a component, two points are awarded; if no major criteria is present but at least one minor criteria is, one point is awarded. Multiple criteria in the same domain do not increase the score. Points are additive only across different domains: major and minor criteria in the same component are not cumulative. Criteria used in the scoring system are listed in Table 1.

Transthoracic Echocardiographic Examination

TTE was conducted using a General Electric (GE) Vivid E9 imaging system (GE Medical Systems, Chicago, USA). Echocardiographic measurements were taken according to the 2015 guidelines, provided by the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI).[8] Left ventricular diameters were measured using M-mode in parasternal long-axis views. Left ventricular ejection fraction (EF) was determined using the biplane modified Simpson method, based on measurements from apical four- and two-chamber views (EF % = Stroke Volume / LV end-diastolic volume × 100). The E/e' ratio was calculated by averaging septal and lateral e' values, in accordance with guideline recommendations.[8,9]

Table 1. HFA-PEFF diagnostic algorithm[4]

Functional	Morphological	Biomarker
Major criteria		
Septal e' < 7 cm/s or lateral e' < 10 cm/s or Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP > 35 mmHg)	LAVi > 34 ml/m² or LVMI ≥ 149/122 g/m² (m/f) and RWT > 0.42	Sinus Rhythm: NT-proBNP > 220 pg/ml or BNP > 80 pg/ml Atrial Fibrillation: NT-proBNP > 660 pg/ml or BNP > 240 pg/ml
Minor criteria		
Average E/e' 9-14 or GLS < 16%	LAVi 29-34 ml/m² or LVMI ≥ 115/95 g/m² or RWT > 0.42 or LV wall thickness ≥ 12 mm	Sinus Rhythm: NT-proBNP 125-220 pg/ml or BNP 35-80 pg/ml Atrial Fibrillation: NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml

DD, Diastolic dysfunction; EF, Ejection fraction; HFpEF, Heart failure with preserved ejection fraction; HF, Heart failure; LAVi, Left atrial volume index; LV, Left ventricle; NT-proBNP, N terminal prohormone of brain natriuretic peptide; RV, Right ventricle; TR, Tricuspid regurgitation.

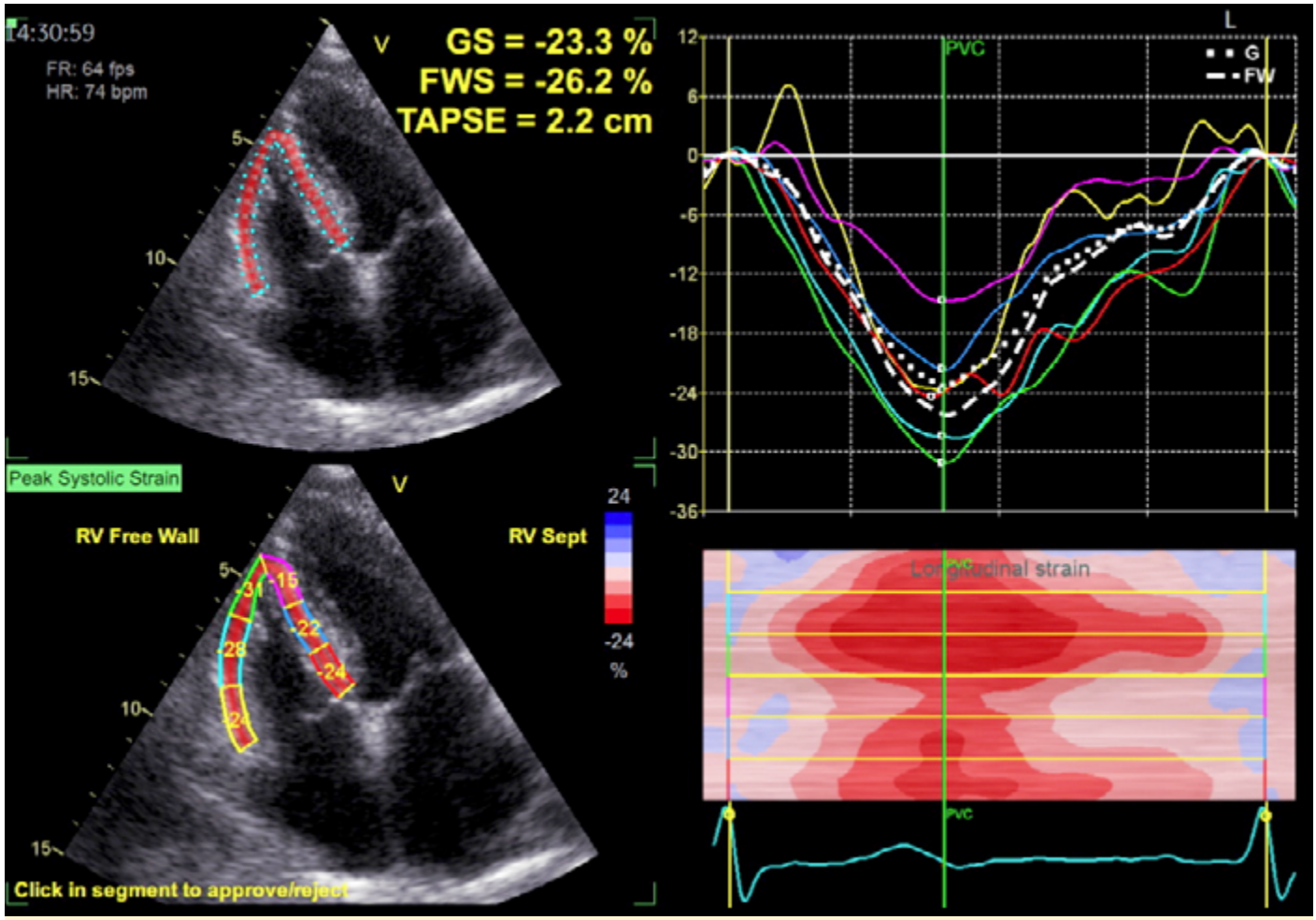

Figure 1. Example of RV 2D strain, TAPSE and tricuspid annular S velocity measurements.

GS, Global strain; FWS, Free wall strain; TAPSE, Tricuspid annular plane systolic excursion, RV, Right ventricular.

Left atrial volume was assessed from apical four-chamber views and indexed to body surface area (LAVi in mL/m²).

2D Speckle Tracking Longitudinal Strain Measurement of the Left and Right Ventricles

RVFW GLS% and LV GLS% were evaluated using 2D speckle tracking based on ASE/EACVI consensus recommendations from 2015 and 2018.[10,11] Apical four-, three- and two-chamber views were used for LV analysis using Automated Function Imaging (AFI). Care was taken to avoid apical foreshortening. Images with well-defined endocardial borders were selected and the region of interest (ROI) was adjusted to cover the myocardium, without spilling into the endocardium or epicardium. For RV assessment, focused RV or apical four-chamber views without foreshortening

Table 2. Baseline characteristics divided by HFA-PEFF score

Characteristics	Total	Score 0-2 (n = 26)	Score 3-4 (n = 43)	Score 5-6 (n = 58)	P
Age, years	64 ± 10	62 ± 9	65 ± 9	65 ± 10	0.5
Female %	69 (54)	12 (46)	22 (51)	35 (60)	0.4
BMI	25 ± 2.6	25.3 ± 2.7	25.3 ± 2.6	24.5 ± 2.4	0.4
HT (%)	83 (65)	16 (62)	27 (63)	40 (69)	0.7
DM (%)	45 (35)	13 (50)	13 (30)	19 (33)	0.2
HL (%)	55 (43)	12 (46)	16 (37)	27 (47)	0.6
Smoking %	69 (54)	15 (58)	25 (58)	29 (50)	0.7
Atrial Fibrillation %	26 (21)	5 (19)	5 (12)	16 (28)	0.1
Medication					
ACE inhibitors/ ARB (%)	65 (51)	12 (46)	25 (58)	28 (48)	0.5
Beta blocker (%)	98 (77)	22 (85)	35 (81)	41 (71)	0.3
Statin (%)	73 (58)	20 (77)	21 (49)	32 (55)	0.07
Oral antidiabetic drug*	59 (47)	12 (46)	20 (47)	27 (47)	1
SGLT2 inhibitor	45 (35)	8 (31)	17 (40)	20 (35)	0.7
Insulin	55 (43)	12 (46)	18 (42)	25 (43)	0.9
Laboratory result					
FPG mg/dl	113.8 ± 50.3	122.5 ± 60.1	114.9 ± 58.9	109.1 ± 37.2	0.9
Hemoglobin g/dl	14.3 ± 1.7	14.3 ± 1.8	13.8 ± 1.8	14.5 ± 1.6	0.2
Creatine (mg/dl)	0.9 ± 0.2	0.9 ± 0.27	0.93 ± 0.21	0.92 ± 0.22	0.9
TC, mg/dl	177.4 ± 38.5	183.4 ± 35.9	179.3 ± 44.9	173.2 ± 34.5	0.5
TG, mg/dl	129 ± 41	125.2 ± 39.4	116.7 ± 40	139.8 ± 40.3	0.9
LDL-C, mg/dl	111 ± 38.2	122.3 ± 40.6	108.7 ± 35.1	107.5 ± 39	0.2
NT-proBNP pg/ml	231.9 ± 194.1	86.7 ± 41.3	169 ± 183.6	343.7 ± 179.8	0.000
Echocardiography					
LVEDD mm	49.6 ± 5.6	50.8 ± 5.6	48.1 ± 6	50.3 ± 5.2	0.08
LVESD mm	28.1 ± 4.3	30.2 ± 4.5	27.5 ± 4.7	27.6 ± 3.6	0.02
LVMI g/m^2	113.4 ± 26.9	111.1 ± 26.9	105.1 ± 27	120.5 ± 25.3	0.01
RWT	0.44 ± 0.9	0.4 ± 0.1	0.45 ± 0.1	0.45 ± 0.1	0.3
EF%	57.1 ± 3.6	57.6 ± 3.8	56.1 ± 3.4	57.5 ± 3.5	0.1
E/e	11.9 ± 3.7	10 ± 2.6	11.3 ± 3.1	13.3 ± 3.9	0.000
LV GLS %	17.1 ± 2.9	18.6 ± 2.5	18.1 ± 2.4	15.8 ± 2.9	0.000
LAVi ml/m^2	33 ± 5.9	29.2 ± 3.9	32.9 ± 4.8	34.7 ± 6.7	0.000
TR jet velocity m/sn	2.6 ± 0.6	2.03 ± 0.5	2.7 ± 0.6	2.7 ± 0.6	0.000
TAPSE mm	16.9 ± 2.9	18.1 ± 3.5	17.9 ± 2.6	15.7 ± 2.3	0.04
Tricuspid annular S velocity cm/sn	11.8 ± 2.7	11.6 ± 3	12.4 ± 2.7	11.4 ± 2.6	0.2
RVFW GLS %	17.2 ± 2.6	19.2 ± 2.6	17.7 ± 2.2	15.8 ± 2	0.000

Values are reported as means±SD, as n (%)* Metformin-GLP-1 receptor agonist. ACE inhibitor/ARB, angiotensin converting enzyme inhibitor/Angiotensin receptor blocker; BMI, Body mass index; DM, Diabetes mellitus; EF, Ejection fraction; FPG, Fasting plasma glucose; HL, Hyperlipidemia; HT, Hypertension; LDL-C, Low-density cholesterol level; LVEDD, Left ventricular end-diastolic diameter, LVESD, Left ventricular end-systolic diameter; LVMI, Left ventricle mass index; LV GLS, Left ventricular global longitudinal strain; P, Probability; RVFW GLS, RV free wall longitudinal strain; RWT, Relative wall thickness; SGLT, Sodium glucose co-transporter 2; TAPSE, Tricuspid annular plane systolic excursion; TC, Total cholesterol; TG, Triglyceride.

and with clearly defined endocardial borders were used (Figure 1). All three segments (basal, mid and apical) of the RV free wall were required to have valid tracking. Images with poorly defined endocardium or missing segmental data were excluded. The ROI was adjusted specifically for RV myocardium. Both LV GLS% and RVFW GLS% values ≤ -20% were considered normal.

Statistical Analysis

In this study, categorical variables were reported as percentages, while numerical data is presented as mean ± standard deviation. Spearman's correlation analysis was conducted to explore the relationship between right ventricular (RV) echocardiographic parameters and the HFA-PEFF score. Patients were categorized

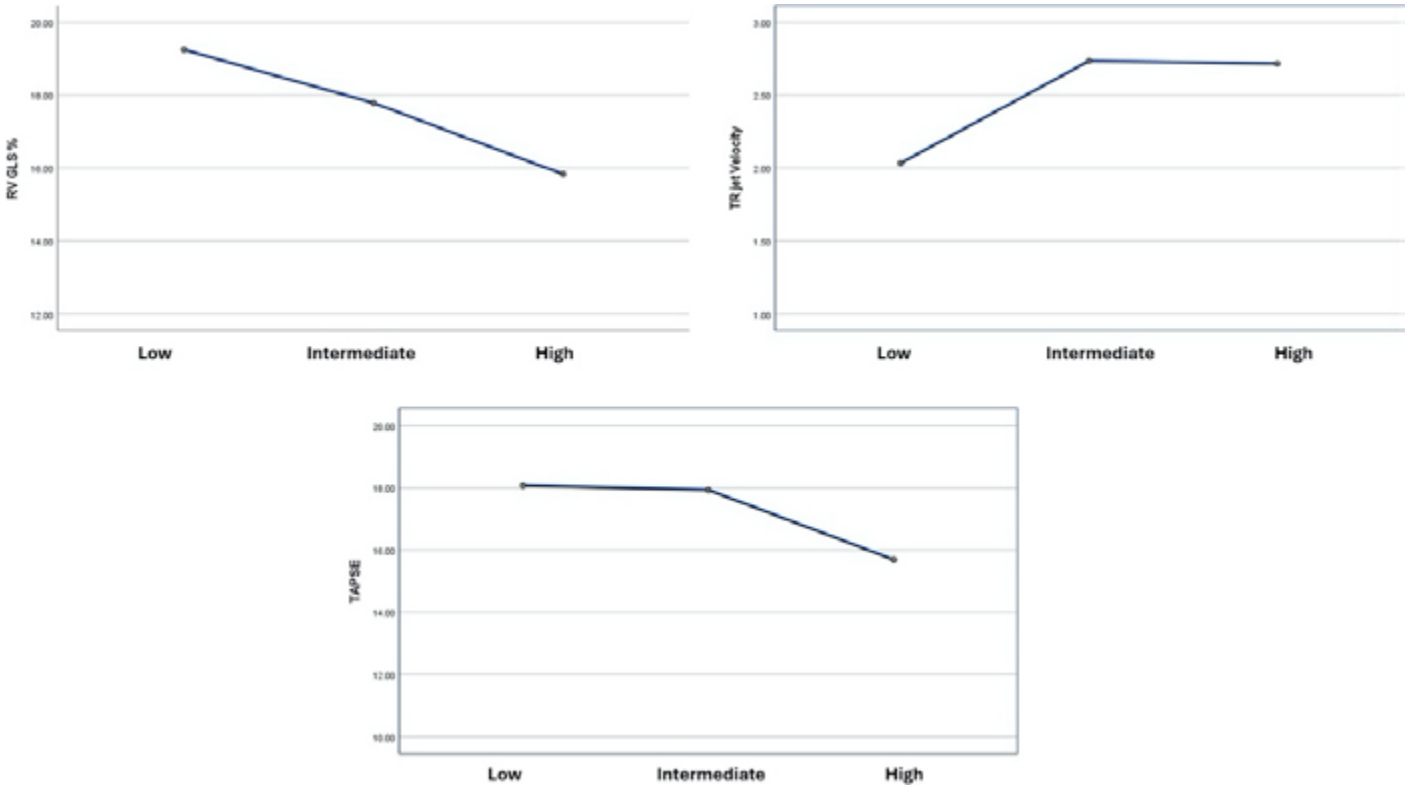

Figure 2. Post-hoc ANOVA analysis of repeated measures of RV GLS, TAPSE and TR jet velocity in three groups: Significant impairment in both TAPSE and RV 2D strain in the high-risk group compared to low- and intermediate-risk groups.

into three prognostic risk groups based on their HFA-PEFF scores: low (0–2), intermediate (3–4) and high (5–6). The differences in demographic, clinical, laboratory and echocardiographic parameters among the three groups were analysed using one-way ANOVA test. The Kruskal-Wallis test was employed for variables with non-normal distribution. Scheffé's post hoc test was used for further subgroup comparison. All statistical analyses were conducted using the IBM SPSS Statistics version 26 (SPSS Inc., Chicago, Illinois). A p-value of less than 0.05 was considered to indicate statistical significance.

Results

The study included 127 patients who had been previously hospitalized at our clinic with a diagnosis of HFpEF and had suitable echocardiographic images. The mean age of the patients was 64 ± 10 years and 69 of them were female (54%). Table 2 summarizes the demographic characteristics, medication use, laboratory findings and echocardiographic parameters of the study population.

For the purpose of prognostic assessment, patients were stratified based on the HFA-PEFF score into three groups: Patients with a score of five or more were classified as high-risk, those with a score of three to four as intermediate-risk and those with a score equal or less than two as low-risk. There were 58 patients in the high-risk group, 43 in the intermediate-risk group and 26 in the low-risk group.

When demographic, laboratory and TTE parameters were compared among the three groups, parameters used in the HFA-PEFF scoring system showed significant differences, which was expected as they are part of the scoring algorithm. In addition to these parameters, the following also showed significant differences among the groups: [Left ventricular end-systolic diameter (LVESD) mm: (low: 30.2±4.5 vs. medium: 27.5±4.7 vs. high: 27.6±3.6; P = 0.02)], [Tricuspid annular plane systolic excursion (TAPSE) mm: (low: 18.1±3.5 vs. medium: 17.9±2.6 vs. high: 15.7±2.3; P = 0.04)], [RV GLS %: (low: -19.2±2.6 vs. medium: -17.7±2.2 vs. high: -15.8±2.0; P < 0.001)].

Post hoc analysis was conducted to determine which specific groups differed (Table 3). The RVFW GLS% was markedly reduced in the high-risk group relative to the low- and intermediate-risk groups (low vs. high: -19.2±2.6 vs. -15.8±2.0; P < 0.001), (medium vs. high: -17.7±2.2 vs. -15.8±2.0; P < 0.001). Similarly, TAPSE values were notably lower in the high-risk group (low vs. high: 18.1±3.5 vs. 15.7±2.3; P = 0.001), (medium vs. high: 17.9±2.6 vs. 15.7±2.3; P < 0.001) (Table 3, Figure 2).

Correlation Analysis

To explore the association between the HFA-PEFF score and right ventricular (RV) echocardiographic parameters, the Spearman correlation analysis was performed. A moderate inverse correlation was identified between the HFA-PEFF score and RV free wall global longitudinal strain (RVFW GLS) (r = –0.50; P < 0.001), as well as between the score and TR jet velocity (r = –0.41; P < 0.001). In addition, a weak negative correlation was detected between the score and TAPSE (r = –0.35; P < 0.001) (Table 4).

Table 3. Intergroup differences in clinical parameters based on HFA-PEFF score (post-hoc analysis)

Variables	HFA-PEFF (0–2) low	HFA-PEFF (3–4) intermediate	HFA-PEFF (5–6) high	P value low vs. intermediate	P value low vs. high	P value intermediate vs. high
NT-proBNP pg/ml	86.7 ± 41.3	169 ± 183.6	343.7 ± 179.8	0.13	0.000	0.000
LVESD mm	30.2 ± 4.5	27.5 ± 4.7	27.6 ± 3.6	0.03	0.03	1
E/e'	10 ± 2.6	11.3 ± 3.1	13.3 ± 3.9	0.3	0.000	0.03
LAVi ml/m^2	29.2 ± 3.9	32.9 ± 4.8	34.7 ± 6.7	0.03	0.000	0.3
LVMI g/m^2	111.1 ± 26.9	105.1 ± 27	120.5 ± 25.3	0.7	0.3	0.02
TR jet velocity m/sn	2.03 ± 0.5	2.7 ± 0.6	2.7 ± 0.6	0.000	0.000	0.000
TAPSE mm	18.1 ± 3.5	17.9 ± 2.6	15.7 ± 2.3	1	0.001	0.000
LV GLS %	18.6 ± 2.5	18.1 ± 2.4	15.8 ± 2.9	0.7	0.000	0.000
RVFW GLS %	19.2 ± 2.6	17.7 ± 2.2	15.8 ± 2	0.3	0.000	0.000

HFA-PEFF, Heart failure association pre-test assessment, echocardiography and natriuretic peptides, functional testing and final etiological diagnosis; NT-proBNP, N terminal prohormone of brain natriuretic peptide; LVESD, Left ventricular end-systolic diameter; LAVI, Left atrial volume index; LVMI, Left ventricle mass index; TR, Tricuspid regurgitation; TAPSE, Tricuspid annular plane systolic excursion; LV GLS, Left ventricular global longitudinal strain; RVFW GLS, RV free wall longitudinal strain.

Discussion

In our study, in addition to conventional echocardiographic measures used to assess right ventricular (RV) function, we also utilized RVFW GLS. When classifying cases into low, intermediate and high prognostic risk groups assigned by the HFA-PEFF score, we found that the group with higher scores "indicating poorer prognosis" had significantly impaired RVFW GLS and TAPSE values compared to the lower-risk groups. Furthermore, a fair correlation was observed between the HFA-PEFF score and RVFW GLS, suggesting that higher scores are associated with greater RV dysfunction as determined by both RVFW GLS and TAPSE.

It is widely recognized that HFpEF is a multifaceted clinical condition marked by hallmark features of heart failure, a left ventricular ejection fraction exceeding 50% and indicators of diastolic dysfunction—such as impaired myocardial relaxation, elevated filling pressures and increased ventricular stiffness.[3] Diastolic dysfunction is regarded as the central pathophysiological mechanism in HFpEF and invasive hemodynamic measurements remain the benchmark for assessing left ventricular filling pressures. However, due to their limited practicality and invasive nature have made TTE the most widely used to estimate LV filling pressure.[9] Parameters such as the E/e′ ratio, TR jet velocity and left atrial volume index (LAVi) are recommended by current guidelines for evaluating LV filling pressures.[9] The latest consensus also suggests that left atrial strain as a useful parameter particularly in patients with inconclusive findings.[12]

To reduce diagnostic ambiguity and develop a more inclusive diagnostic system, the ESC Heart Failure Association introduced the HFA-PEFF algorithm in 2019 4, which was later validated in multiple studies for its diagnostic utility.[13,14] Subsequent studies investigated its prognostic significance.[5,15] For example, Egashira et al.[16] demonstrated that a cut-off value of 4.5 on the HFA-PEFF score could identify HF-related adverse events beyond conventional prognostic indicators. Similarly, a meta-analysis confirmed the score's diagnostic and prognostic value, including its ability to predict overall mortality in HFpEF patients.[5] A 2022 study in ESC Heart Failure found that the HFA-PEFF score was found to be significantly associated with all-cause mortality and heart failure rehospitalizations in HFpEF patients, after transcatheter aortic valve implantation (TAVI), suggesting the score's potential role in risk stratification for TAVI patients.[17] In our study, according to studies outlined above, we used the HFA-PEFF score as a prognostic tool in HFpEF patients, categorizing the study population into three subgroups accordingly.

Table 4. Correlation between RV echo parameters and HAF-PEFF

Variables	r	P
TAPSE	-0.35	0.000
Tricuspid annulus S velocity	-0.08	0.3
TR peak velocity m/sec	-041	0.000
RV GLS%	-0.5	0.000

R, Correlation coefficient. TAPSE, Tricuspid annular plane systolic excursion; TR, Tricuspid regurgitation; RV GLS, Right ventricular global longitudinal strain.

The RV is significantly affected in HFpEF and RV dysfunction is known to be related to poorer prognosis in these patients.[7,18] Contrary to earlier assumptions, RV dysfunction can occur early in HFpEF due to increased pressures in the pulmonary vasculature.[19] Nagueh et al.[20] showed a strong correlation between estimated right atrial pressure via TTE and invasively measured pulmonary capillary wedge pressure (sensitivity 76%, specificity 86%). Similarly, Mele et al.[21] found a strong relationship between mean right atrial pressure and pulmonary capillary wedge pressure in patients with indeterminate left atrial pressure, as determined by the 2016 ASE/EACVI guidelines, attributing RV dysfunction to early pressure overload in the thin-walled RV.

In an animal study, the TAPSE/sPAB (systolic pulmonary artery pressure) ratio—a key indicator of RV-PA (pulmonary artery) coupling—was significantly reduced in HFpEF and showed strong correlation with invasively measured pulmonary vascular resistance.[22] This ratio provides crucial information about RV contractile function and the study revealed that even slight increases in mean pulmonary artery pressure in early HFpEF, can

impair RV function through passive pressure fluctuations in the pulmonary vasculature.[23] Despite these important findings, RV functional parameters are still not incorporated into diagnostic and prognostic algorithms for HFpEF.

With the increasing use of strain imaging, 2D speckle tracking has become a routinely employed technique to assess RV systolic function. Evaluating RV systolic function via TTE is challenging and cardiac magnetic resonance imaging is widely regarded as the primary reference for RV EF.[24,25] However, the 2D strain technique is a sensitive, accessible and reproducible method that can detect subclinical dysfunction, even in the absence of RV dilation. RVFW GLS has been shown in numerous studies to have prognostic value.[26,27] We believe that in addition to traditional RV parameters, RVFW strain is a reliable marker capable of identifying early signs of dysfunction in patients without overt RV impairment. In our study, we therefore examined the relationship between RVFW strain and the HFA-PEFF score.

Ultimately, we found that RVFW GLS and TAPSE values were markedly impaired in the high-score (i.e., poor prognosis) group and RVFW GLS demonstrated intermediate correlation with the HFA-PEFF score. Based on these findings, we believe that incorporating TAPSE and RVFW GLS into diagnostic and prognostic algorithms used for HFpEF patients, could enhance the diagnostic accuracy and clinical utility of these tools.

Study Limitations

Several limitations must be acknowledged in this study. To begin with, the retrospective design and the modest sample size may affect the robustness of the findings. Additionally, due to its retrospective nature, TTE measurements were obtained either on the day of or the day prior to hospital discharge. Although these patients were assumed to be in a compensated (euvolemic) state, their volume status was not definitively known. It is well established that volume overload can influence diastolic parameters and right ventricular strain measurements. Despite these limitations, our study demonstrates that TAPSE and RVFW GLS values were significantly impaired in the poor prognosis group as defined by the HFA-PEFF algorithm, compared to other groups.

Conclusion

In our study, both RVFW GLS (%) and TAPSE values were notably diminished in patients with HFA-PEFF scores of five and six, indicating poor prognosis. Despite the limited number of participants, our results yield an important contribution to a topic with scarce data in the literature. These results highlight the need for larger, prospective studies to further validate our conclusions.

Ethics Committee Approval: Ethics committee approval was obtained from Ankara University Faculty of Medicine Human Research Ethics Committee (Approval Number: İ1-22-21, Date: 14.01.2021).

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Implications of Procedure of Thoracic Endovascular Aortic Repair on Left Ventricular Global Longitudinal Strain

Torasik Endovasküler Aort Onarımı Prosedürünün Sol Ventrikül Global Longitudinal Strain Üzerine Etkisi

ABSTRACT

Objective: The aorta, particularly in its proximal segments, expands during systole to store blood, which is subsequently released into the peripheral circulation during diastole, morphologically and histologically. This function, referred to as the "Windkessel effect," ensures continuous and regular blood flow in the peripheral circulation. Thoracic Endovascular Aortic Repair (TEVAR) was introduced in the literature as a treatment for Type B aortic dissections (TBAD). In patients who undergo TEVAR, the placement of a stent graft in the proximal segments of the aorta, which are responsible for the highest capacity of blood storage and elasticity, may disrupt this function. Consequently, this alteration may lead to increased afterload and, over the long term, impair left ventricular systolic function. Previous studies have demonstrated that measurements of left ventricular global longitudinal strain (LVGLS) can detect early systolic dysfunction before any significant changes in left ventricular ejection fraction (LVEF) occur. The aim of this study was to compare preoperative and postoperative LVGLS measurements in patients who underwent TEVAR, thereby illustrating changes in LVGLS associated with the procedure.

Method: Patients who underwent TEVAR for TBAD or Thoracic Aortic Aneurysm (TAA) were included in the study. Patients with malignancy, advanced valvular pathology, end-stage chronic kidney disease, liver failure or heart failure, were excluded. Preoperative data, including comorbidities, medication use, blood parameters, electrocardiography findings, transthoracic echocardiography images and LVGLS values, were recorded. These parameters were then compared with the values obtained at the postoperative three-month outpatient follow-up.

Results: After the TEVAR procedure, a significant decrease in LVGLS was observed ($P < 0.001$). A strong correlation was found between the change in mean arterial pressure (MAP) and the reduction in LVGLS ($P = 0.555$, $P = 0.017$). Postoperatively, significant increases were noted in systolic blood pressure (SBP) and MAP (both $P < 0.001$). No significant differences were observed in other parameters, before and after the procedure.

Conclusion: In our study, a significant increase in SBP and MAP, along with a notable decrease in LVGLS values, were observed following the TEVAR procedure. A significant and strong correlation was identified between the increase in MAP and the decrease in LVGLS.

Keywords: Aortic compliance, global longitudinal strain, thoracic endovascular aortic repair, Windkessel effect

ÖZET

Amaç: Aort, özellikle proksimal segmentlerinde, sistol sırasında genişleyerek kanı depolar ve diyastol sırasında bu kanı periferik dolaşıma iletir. Bu morfolojik ve histolojik özellik "Windkessel etkisi" olarak adlandırılan bu fonksiyon periferik dolaşımda sürekli ve düzenli kan akışını sağlar. Tip B aort diseksiyonlarının (TBAD) tedavisi için literatüre Torasik Endovasküler Aort Onarımı (TEVAR) yöntemi girmiştir. TEVAR uygulanan hastalarda, kan depolama kapasitesi ve kompliyansı en yüksek olan proksimal aort segmentlerine stent greft yerleştirilmesi bu fonksiyonu bozabilir. Bu değişiklik, artmış ard yük ile sonuçlanarak uzun vadede sol ventrikül sistolik fonksiyonlarını olumsuz etkileyebilir. Önceki çalışmalar, sol ventrikül ejeksiyon fraksiyonunda (LVEF) belirgin bir değişiklik olmadan önce, sol ventrikül global longitudinal strain (LVGLS) ölçümlerinin erken sistolik disfonksiyonu tespit edebildiğini göstermiştir. Bu çalışmanın amacı, TEVAR uygulanan hastalarda preoperatif ve postoperatif LVGLS ölçümlerini karşılaştırarak, prosedüre bağlı olarak LVGLS'de meydana gelen değişiklikleri ortaya koymaktır.

Yöntem: Çalışmaya TBAD veya Torasik Aort Anevrizması (TAA) nedeniyle TEVAR uygulanmış hastalar dahil edilmiştir. Malignite, ileri derecede kapak hastalığı, son evre kronik böbrek yetmezliği, karaciğer yetmezliği veya kalp yetmezliği bulunan hastalar çalışma dışı bırakılmıştır.

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Hastaların preoperatif döneme ait komorbiditeleri, ilaç kullanımları, kan parametreleri, elektrokardiyografi bulguları, transtorasik ekokardiyografi görüntüleri ve LVGLS değerleri kaydedilmiştir. Bu parametreler, postoperatif 3. ay poliklinik kontrollerinde elde edilen verilerle karşılaştırılmıştır.

Bulgular: TEVAR işlemi sonrası LVGLS'de anlamlı bir azalma gözlenmiştir ($P < 0.001$). Ortalama arter basıncındaki (OAB) değişim ile LVGLS azalması arasında güçlü bir korelasyon saptanmıştır ($P = 0.555$, $P = 0.017$). Postoperatif dönemde sistolik kan basıncı (SKB) ve OAB değerlerinde belirgin artış tespit edilmiştir (her ikisi için $P < 0.001$). İşlem öncesi ve sonrası diğer parametrelerde anlamlı bir fark bulunmamıştır.

Sonuç: Çalışmamızda, TEVAR işlemi sonrasında SKB ve OAB'de belirgin bir artış ile birlikte LVGLS değerlerinde anlamlı bir azalma saptanmıştır. Ayrıca, OAB artışı ile LVGLS azalması arasında güçlü ve anlamlı bir ilişki olduğu gösterilmiştir.

Anahtar Kelimeler: Aort kompliansı, global longitudinal strain, torasik endovasküler aort onarımı, Windkessel etkisi

Thoracic endovascular aortic repair (TEVAR) has been introduced as an interventional treatment to the literature and is a well-established procedural technique for the management of type B aortic dissection.[1,2] Despite improvements in technology and techniques, including enhancements in biomedical graft materials, imaging techniques, implantation, and procedural techniques, stent-graft implantation in the aorta increases the stiffness of the aorta.[3] One study demonstrated that TEVAR has this effect and leads to myocardial dysfunction in young patients who underwent TEVAR as a result of a blunt thoracic aortic injury, in the previous five years.[4] Moreover, it has been shown that using endografts with different types of fabrics in the endovascular aortic repair (EVAR) procedure, also resulted in increased aortic stiffness.[5] Another study confirmed this finding and showed that endograft implantation during the EVAR procedure in the aorta increases the stiffness of the aorta, when compared to open surgical repair.[6] In an experimental study on a porcine model, researchers showed that implantation of an endograft during the TEVAR procedure in the aorta decreased the strain of the aorta.[7] Based on these studies, we can see that there is limited knowledge about the potential effects of these grafts on aortic stiffness and their impact on heart function. Thus the effects of increased arterial stiffness after EVAR and TEVAR on the heart and central hemodynamic, as well as their eventual effect on cardiac systolic function, need to be further investigated and evaluated.[8,9]

ABBREVIATIONS

2D STE	Two-dimensional speckle-tracking echocardiography
COPD	Chronic obstructive pulmonary disease
DM	Diabetes mellitus
ECG	Electrocardiography
EVAR	Endovascular aortic repair
HT	Hypertension
LA	Left atrial
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVGLS	Left ventricular global longitudinal strain
MAP	Mean arterial pressure
MRI	Magnetic resonance imaging
NT-pro BNP	N-terminal pro-Brain Natriuretic Peptide
PTFE	Polytetrafluoroethylene
RV	Right ventricle
RV GLS	RV global longitudinal strain
SBP	Systolic blood pressure
TAA	Thoracic Aortic Aneurysm
TBAD	Type B aortic dissections
TDI	Tissue Doppler imaging
TEVAR	Thoracic Endovascular Aortic Repair

Arterial stiffness has been closely associated with myocardial function, and left ventricular global longitudinal strain (LVGLS) is a powerful method for identifying left ventricular (LV) function.[10,11] Papadopoulos et al.[12] published one of the first case reports when they investigated the changes in LVGLS after the EVAR procedure in a patient and found that none of the echocardiographic parameters were deteriorated after the procedure, except for LVGLS. In their next study, they found that LVGLS deteriorated even in the early post-procedural follow up of these patients, after the EVAR procedure.[13] In order to address these questions, we designed this study with the aim to investigate the possible hemodynamic and LVGLS changes after the procedure of TEVAR and the possible changes associated with aortic stiffness.

Materials and Methods

Study Population and Demographics

Our study was performed with a prospective cohort and eighteen patients were included. It was conducted following ethical approval by the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital Ethical Committee (Approval Number: 2023.01-81, Date: 24.10.2023), between March 2023 and May 2024, in a tertiary referral hospital.

Patients over the age of eighteen who underwent the TEVAR procedure and provided their informed consent were included in the study. Patients with left ventricular ejection fraction (LVEF) < 35%, moderate-to-severe valvular heart disease, or end-stage kidney disease or a diagnosis of malignancy, were excluded from the study. It was conducted in accordance with the Declaration of Helsinki and no AI-assisted technology was used at any stage.

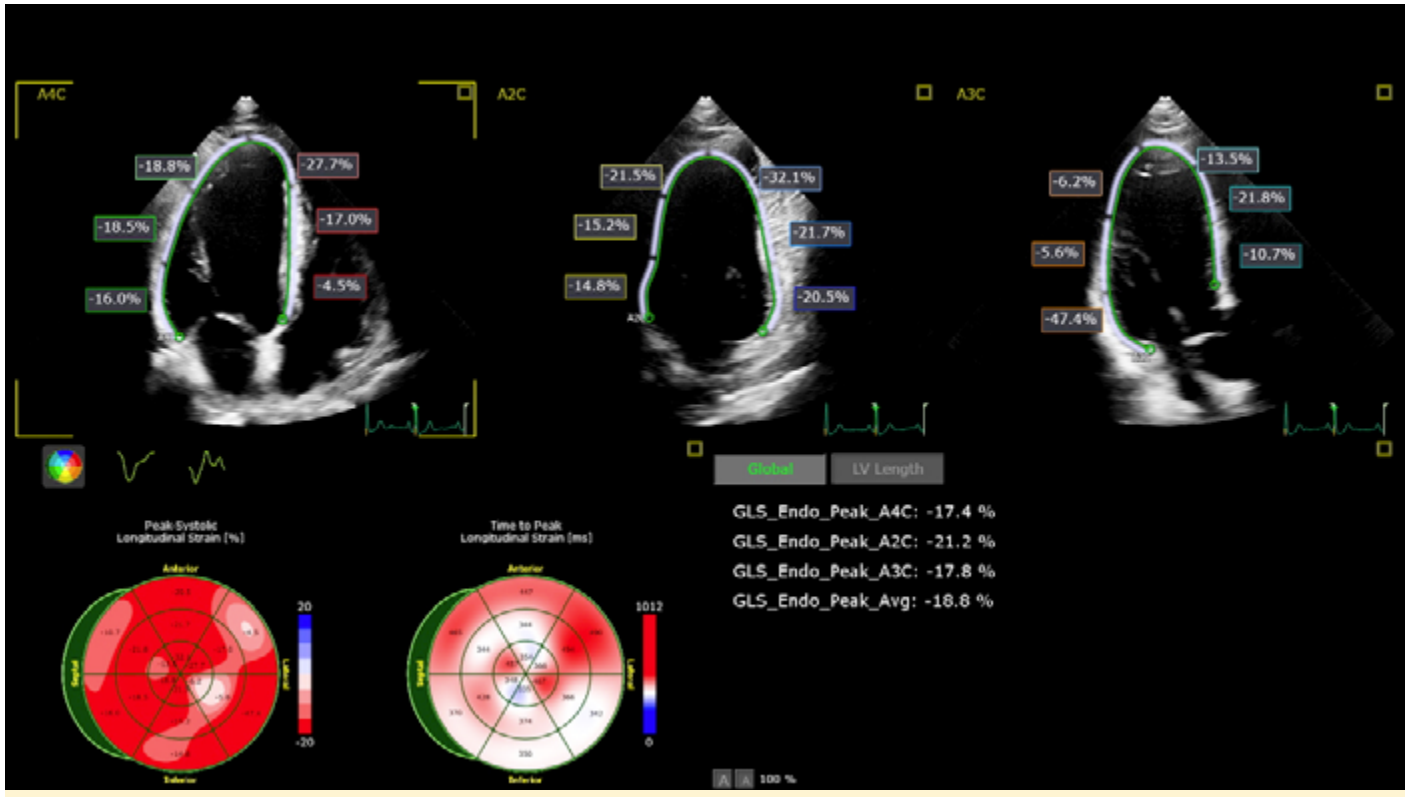

Figure 1. Left ventricular global longitudinal strain analysis using speckle-tracking echocardiography.

The demographic data, preoperative medication use, comorbid conditions, laboratory results, and both electrocardiography (ECG) and echocardiographic measurements of the enrolled patients were documented. Data including age, gender, presence of comorbid diseases such as hypertension (HT), hyperlipidemia, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), kidney disease (not an end-staged) and cerebrovascular disease, were noted for all the patients. ECG recordings were evaluated for heart rate, presence of bundle branch blockage, PR and QRS duration. Laboratory tests included complete blood count, creatinine and N-terminal pro-Brain Natriuretic Peptide (NT-pro BNP). The blood pressure values measured after the patients had rested, prior to the TEVAR procedure were recorded in the patient's file, along with the recorded ECG and variables of the transthoracic echocardiogram. Upon the patient's three-month follow-up visit, the same values were documented.

Echocardiographic Evaluation

The echocardiographic images of all participants were acquired using a Philips EPIQ CVX 3D system (Philips Healthcare, Andover, MA, USA), with an S5-1 transducer (3.5 MHz) for 2-Dimensional (2D) measurements and an X5-1 transducer (1-3 MHz) for 3-Dimensional (3D) measurements. Echocardiographic data included both conventional parameters and strain parameters. Standard M-mode, 2D, Doppler and color-coded tissue Doppler (TDI) images were obtained during a breath hold, stored in cine loop format from three consecutive beats, then transferred to a workstation for further offline analysis. Conventional echocardiographic measurements were performed in accordance with the recommendations of the European Association of Cardiovascular Imaging guidelines.[14] LV, right ventricular (RV), and left atrial (LA) strains were measured for every patient, as described in previous studies.[15-17] The evaluation of LVGLS was conducted using two-dimensional speckle-tracking echocardiography (2D STE), with imaging obtained from the apical two-chamber, three-chamber and four-chamber views of the LV. In each of these apical views, the LV was subdivided into six segments. The LVGLS value was calculated as the average of the peak systolic longitudinal strain values from each of the six segments across all apical views (Figure 1). The LA endocardial border was manually delineated in the apical four-chamber view, integrating the six segments. Following an analysis of the tracking quality for each segment, any necessary manual adjustments were made. Subsequently, strain curves for each atrial segment were generated using the software, which utilized the QRS complex (R-R gating) to initiate the strain calculation. With the use of the R wave, all strain values were recorded as positive. Two distinct peaks were observed: the first, occurring between the R wave and T wave, corresponded to the reservoir function, while the second peak, initiated by the P wave, reflected the atrial contractile function. The difference between the strain values of the reservoir and atrial contractile functions, provides an indication of the conduit function (Figure 2). The RV endocardial borders were traced and fine-tuned manually to ensure that the six segments (basal, middle, and apical of the free wall and interventricular septum), were tracked appropriately, and then time-strain curves were generated for the measurement of RV global longitudinal strain (RV GLS) (Figure 3).

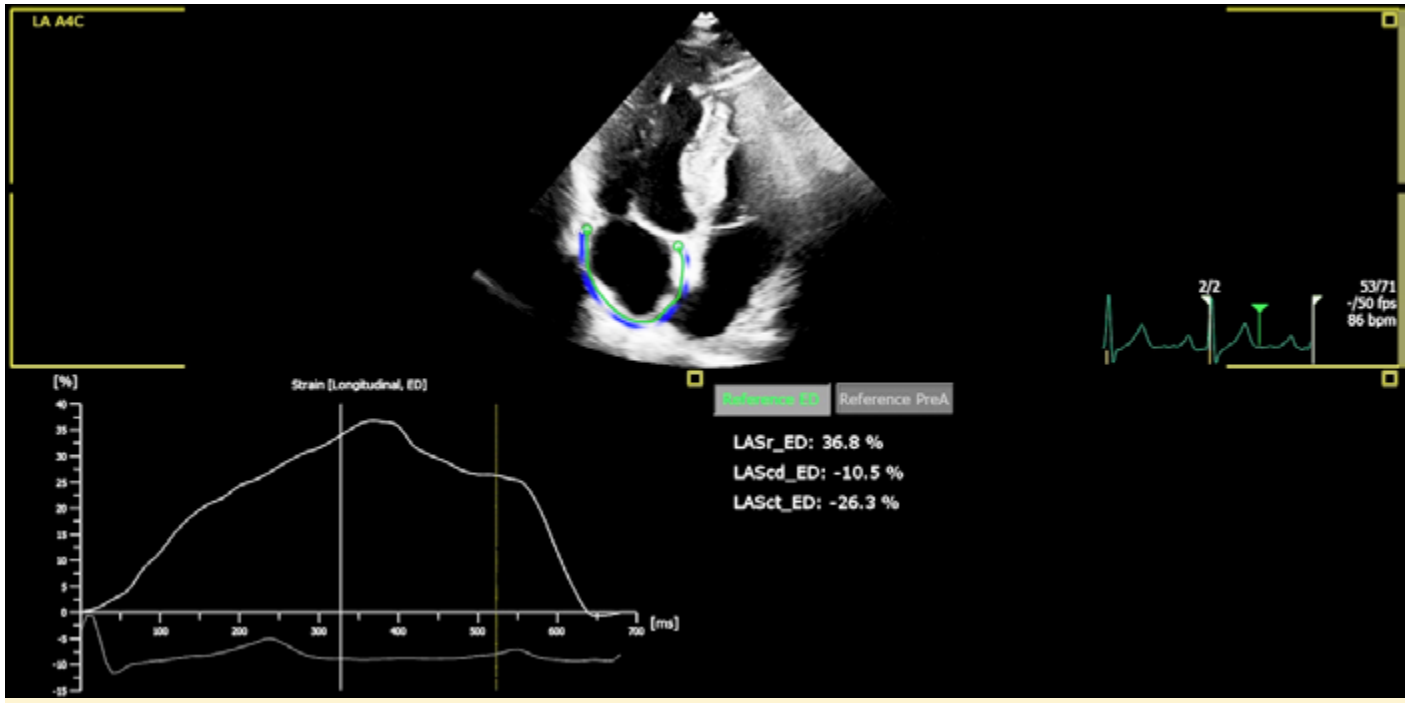

Figure 2. Assessment of left atrial conduit function.

Patients were routinely scheduled for a follow-up visit at the outpatient clinic, three months after the procedure. During this visit, laboratory results, ECG and echocardiographic measurements were reassessed and LVGLS, LA strain and RV GLS values were re-measured, using the same device.

Statistical Analysis

The statistical analysis of the study was conducted using the SPSS Version 27.0 (SPSS Inc., Chicago, Illinois, USA). As the number of patients included in the study was eighteen, numerical variables were presented as median (interquartile range), while categorical variables were expressed as percentages (%). The statistical analysis of numerical variables between groups, such as LVGLS, was performed using the Wilcoxon test and the analysis of categorical variables was conducted using the Mann-Whitney U test. The correlation of LVGLS with other numerical parameters was assessed using Spearman's analysis. The threshold for statistical significance was set at $P < 0.05$.

Results

A total of eighteen patients were included in the study. The median age of the patients was 56.0 years, with eleven of them being male. The demographic and clinical characteristics of the patients, along with their follow-up durations, are summarized in Table 1. Among the patients included in the study, thirteen patients had HT, one patient had DM, three patients had COPD and three patients had coronary artery disease.

Twelve patients (66.67%) were using at least one antihypertensive medication prior to the procedure, whereas after the procedure, sixteen patients (88.89%) were using at least one. The medications used by the patients before and after the procedure are summarized in Table 2.

Table 1. Demographic and clinical characteristic of the study group

Age, years	56.0 (45.5–61.0)
Follow up duration, (days)	107.5 (92.5–126.0)
Male sex, n (%)	11 (61.1)
Hypertension, n (%)	13 (72.2)
Diabetes mellitus, n (%)	1 (5.6)
Chronic obstructive pulmonary disease, n (%)	3 (16.7)
Coronary artery disease, n (%)	3 (16.7)

Table 2. Antihypertensive medication usage of the patients before and after the procedure

	Before procedure n (%)	After procedure n (%)
Angiotensin converting enzyme inhibitors	6 (33.3)	11 (61.1)
Angiotensin receptor blockers	4 (22.2)	3 (16.7)
Beta blockers	10 (55.6)	15 (83.3)
Calcium channel blockers	8 (44.4)	13 (72.2)

The association between clinical and demographic characteristics with LVGLS is shown in Table 3. There was no significant association between demographics, clinical characteristics of the patients and changes in LVGLS, after the procedure. When comparing the patients' medication use before and after the procedure with changes in LVGLS after the procedure, no significant difference was observed between the groups (Table 4).

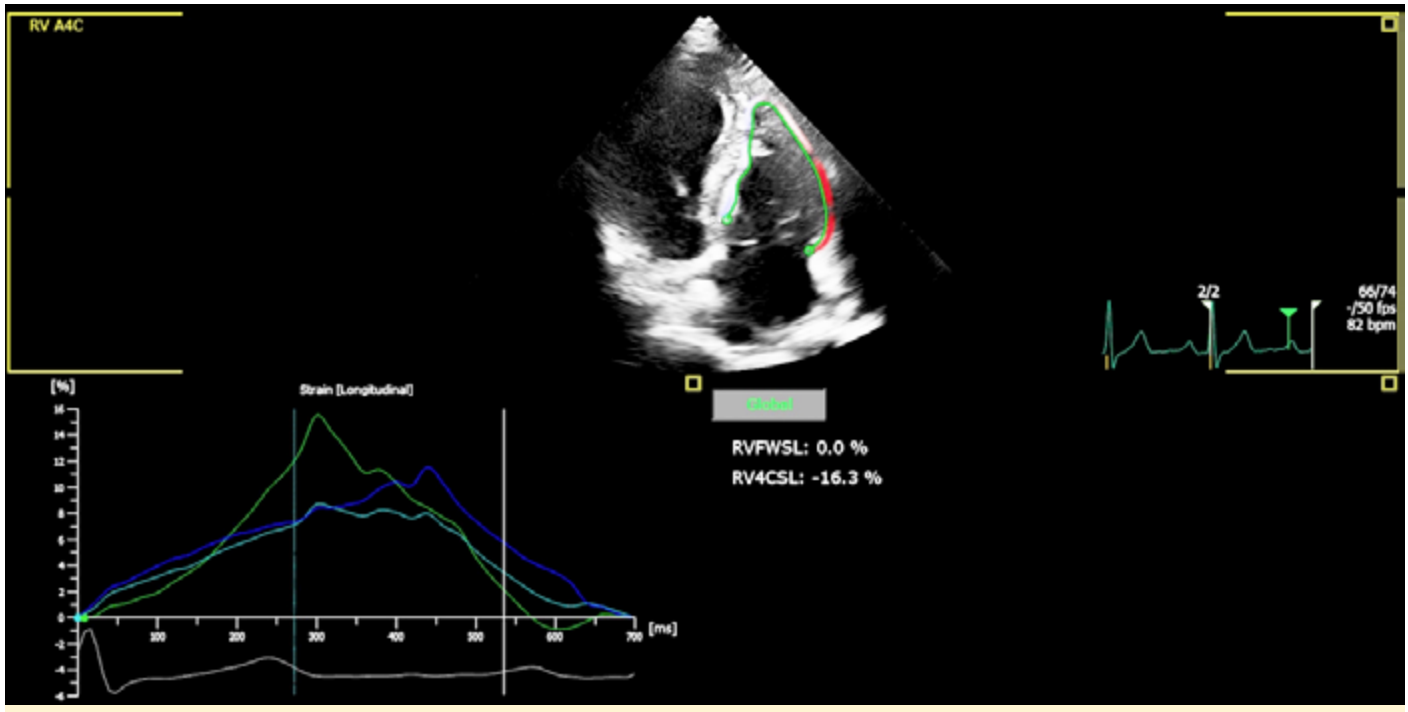

Figure 3. Right ventricular global longitudinal strain (RV GLS) measurement.

Table 3. The association between demographic and clinical characteristics of the patient group and change in left ventricular global longitudinal strain after the procedure

	Change in LVGLS	P
Gender		0.928
Male	1.90 (1.50–4.10)	
Female	2.10 (1.00–6.50)	
Hypertension		0.278
With diagnosis	1.90 (1.15–3.25)	
Without diagnosis	4.10 (1.75–4.50)	
Coronary artery disease		0.109
With diagnosis	1.50 (1.15–1.70)	
Without diagnosis	2.20 (1.70–4.20)	

LVGLS, Left ventricular global longitudinal strain.

Table 4. Change in LVGLS after the procedure in patients under antihypertensive medication and without antihypertensive medication before the procedure

	Change in LVGLS with medication usage	Change in LVGLS without medication usage	P
ACE-Inh	2.80 (1.32–6.50)	1.85 (1.40–3.82)	0.51
ARB	2.05 (1.45–2.80)	1.95 (1.37–4.35)	0.83
BB	1.80 (1.22–3.67)	2.15 (1.80–4.62)	0.35
CCB	1.70 (1.07–5.75)	2.15 (1.77–4.12)	0.66

ACE-inh, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers; BB, beta blockers; CCB, Calcium channel blockers; LVGLS, Left ventricular global longitudinal strain.

The evaluation of ECG recordings and data about blood pressures is summarized in Table 5. No significant difference was observed before and after the procedure regarding heart rate, PR interval and QRS duration on the ECG recordings. Four patients who were not using antihypertensive medication before the procedure were started on antihypertensive treatment, and the antihypertensive therapy of five patients was increased after the procedure. Despite this, a significant increase was observed in the patients' systolic blood pressure and non-invasive mean arterial pressure values post-procedure, compared to pre-procedure values ($P < 0.001$ for both analyses). No significant difference was observed in diastolic blood pressure values before and after the procedure ($P = 0.432$).

The statistical evaluation of the laboratory parameters is shown in Table 6. No significant difference was observed between the laboratory parameters assessed before the procedure and those re-evaluated during the three-month follow-up visit.

The statistical evaluation of the TTE parameters is shown in Table 7. The TTE images obtained before the procedure and those obtained during the three-month follow-up visit were compared. The analysis showed that the LVGLS value after the procedure was significantly lower, compared to pre-procedure values ($P < 0.001$). No significant changes were observed in other TTE parameters. The correlation between the change in LVGLS before and after the procedure and other parameters was evaluated. A significant positive correlation was observed between the change in mean arterial pressure and the change in LVGLS (Figure 4, $P = 0.555$, $P = 0.017$). No significant correlation was found between the change in LVGLS and other parameters.

Table 5. Comparison of ECG parameters and blood pressure measurements before and after the procedure

	Pre-procedural	Post-procedural	P
Heart rate, bpm	73.00 (69.75–86.00)	79.00 (66.75–83.50)	0.896
PR duration, ms	156.00 (146.50–178.50)	152.00 (141.50–174.00)	0.169
QRS duration, ms	88.00 (81.50–98.50)	87.00 (81.50–92.00)	0.142
Systolic blood pressure, mmHg	114.50 (108.75–128.25)	155.00 (146.50–168.00)	< 0.001
Diastolic blood pressure, mmHg	72.00 (64.25–81.50)	73.00 (65.00–85.00)	0.432
Mean arterial blood pressure, mmHg	87.83 (77.25–97.75)	99.50 (93.66–114.58)	< 0.001

ECG, Electrocardiography.

Table 6. Comparison of laboratory parameters before and after the procedure

	Pre-procedural	Post-procedural	P
Hemoglobin, g/dL	11.50 (9.90-12.52)	12.05 (10.20-12.92)	0.276
Leucocytes, /μL	8.09 (7.01-10.30)	7.90 (6.54-9.39)	0.327
Lymphocytes, /μL	1.84 (1.21-2.49)	1.95 (1.48-2.52)	0.463
Neutrophils, /μL	5.36 (4.64-7.39)	4.86 (3.72-6.10)	0.193
Glucose, mg/dL	108.00 (90.50-122.00)	106.50 (88.00-132.25)	0.943
Albumin, g/dL	4.12 (3.62-4.22)	4.13 (3.79-4.41)	0.410
Creatinine, mg/dL	0.98 (0.88-1.26)	0.98 (0.84-1.12)	0.472
Glomerular filtration rate, mL/dk/1,73m^2	71.78 (55.12-97.39)	82.75 (57.18-94.77)	0.711
C-reactive protein, mg/dL	26.25 (6.87-84.25)	15.25 (6.72-34.25)	0.306
Brain natriuretic peptide, pg/mL	231.65 (125.57-1010.52)	177.80 (79.01-577.47)	0.600

Table 7. The comparison of echocardiographic parameters before and after the procedure

	Pre-procedural	Post-procedural	P
Ejection fraction	60.00 (60.00-60.00)	60.00 (60.00-60.00)	0.317
Left ventricular end diastolic diameter	47.50 (45.75-50.00)	48.00 (46.00-52.00)	0.166
Left ventricular end systolic diameter	31.00 (28.75-34.25)	32.00 (30.75-33.25)	0.327
Left atrial diameter	37.50 (34.50-38.25)	37.00 (35.00-39.00)	0.894
Diameter of ascending aorta	36.95 (34.15-39.77)	37.50 (35.70-39.75)	0.593
Diameter of sinus of valsalva	36.30 (33.75-39.50)	36.00 (33.90-39.70)	0.434
TAPSE	22.35 (20.62-25.15)	21.85 (17.95-24.00)	0.133
Tricuspid annular S wave velocity	13.75 (12.27-15.67)	13.10 (11.15-16.20)	0.177
E wave velocity	71.00 (57.75-89.25)	70.50 (57.00-84.25)	0.316
A wave velocity	84.50 (78.00-98.00)	85.00 (72.50-91.00)	0.157
Septal E wave velocity	5.65 (4.59-6.25)	5.15 (4.65-5.40)	0.080
Lateral E wave velocity	7.66 (7.10-9.95)	7.85 (7.27-8.72)	0.446
Left ventricular global longitudinal strain	-15.50 (-17.40,-14.25)	-13.00 (-15.20,-11.30)	< 0.001
Left atrium strain	20.20 (14.30-37.37)	22.00 (14.87-30.27)	0.948
Right ventricular free-wall strain	-16.60 (-18.00,-14.80)	-14.90 (-17.55,-11.00)	0.053

TAPSE, Tricuspid annular plane systolic excursion.

Discussion

Our study investigated the possible changes in strain of the heart after endograft implantation into the aorta, via the TEVAR procedure. Our study showed that endograft implantation into the aorta increased systolic blood pressure, however it did not change diastolic blood pressure after the TEVAR procedure. Moreover, due to the change in afterload and compliance of the aorta, LV functions were also affected after the graft implantation independent of LVEF and our study showed that LVGLS was significantly reduced, after endograft implantation into the aorta. The change in LVGLS was not found to be associated with other morbidities or aging in the study group, which indicates that the procedural change in the aorta was associated with the change in LVGLS.

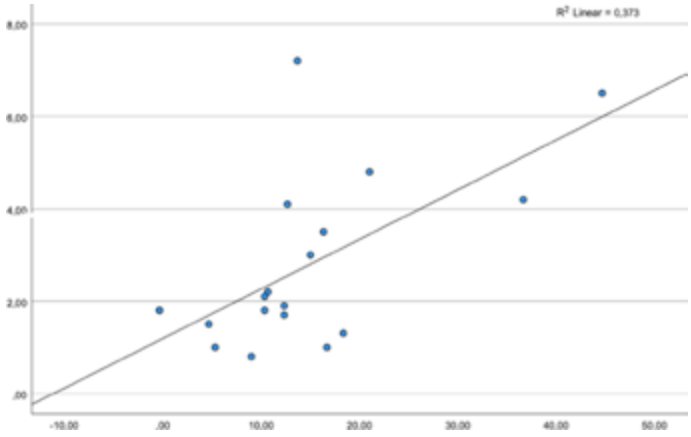

Figure 4. Correlation between change in mean arterial pressure (MAP) and change in left ventricular global longitudinal strain (LVGLS) following the procedure.

It is well known that aortic stents might implicate the compliance of the aorta. Agrafiotis et al.[18] studied thoracic aortic stents in ten patients ex-vivo and their experiment showed that aortic distensibility was significantly reduced after TEVAR, and caused aortic stiffening and mismatch in the compliance of the aorta. In another study, Kadoglou et al.[5] conducted a study, between April 2010 and November 2011, involving 118 patients who underwent abdominal EVAR. The study aimed to compare the outcomes of stent grafts coated with polytetrafluoroethylene (PTFE) and polyester. In this study, 46 patients received PTFE-coated stent grafts, while 72 patients received polyester-coated stent grafts. The assessment of aortic stiffness was performed using pulsed wave velocity in the aorta. The results of the study showed an increase in aortic stiffness when comparing preoperative and postoperative measurements, whereas the comparison between the two types of stent grafts showed no significant difference. Based on these findings, it was concluded that aortic stiffness increased after EVAR, independent of the type of graft used. In another study, Rong et al.[19] showed that aortic circumferential strain and stiffness increased after graft implantation into the aorta. These studies illustrate the close relationship between aortic stenting and aortic compliance, emphasizing how stent implantation affects both the stiffness and compliance of the aorta.

These studies also concluded that endograft implantation leads to a reduction in aortic compliance. This decrease in compliance results in a diminished Windkessel effect, which ultimately causes an increase in arterial stiffness. In previous studies, the increase in arterial stiffness was associated with a rise in systolic blood pressure and a decrease in diastolic blood pressure.[20,21] In our study, systolic blood pressure values were found to be 114.50 (108.75 - 128.25) mmHg before the procedure and 155.00 (146.50 - 168.00) mmHg after the procedure. The mean arterial pressure was 87.83 (77.25 - 97.75) mmHg before the procedure and 99.50 (93.66 - 114.58) mmHg after the procedure. There was a significant increase in both systolic blood pressure and mean arterial pressure after the procedure ($P < 0.001$ for both analyses). No significant change was observed in diastolic blood pressure values ($P = 0.432$). Our results are consistent with the expected outcomes of increased arterial stiffness due to the reduction in aortic compliance.

The reduction in aortic compliance not only affects peripheral circulation and blood pressure but also impacts the increased afterload on LV function. Studies suggest that an increase in afterload may lead to impaired LV function.[22] Impairment of LV function can be detected early with LVGLS, even before changes in LVEF are apparent. Aside from hypokinesis due to ischemic heart disease, LVGLS is also affected by increased afterload from other conditions, making it more effective than LVEF in predicting long-term outcomes.[23,24] In our study, no significant change was observed in LVEF before the procedure and after a median follow-up of 107.5 days. However, LVGLS values were -15.50 (-17.40, -14.25) before the procedure and -13.00 (-15.20, -11.30) after the procedure, and a significant decrease in LVGLS was observed after the procedure. It has been previously demonstrated that EVAR might lead to a decrease in LV functions and deterioration of LVGLS after the procedure. Marketou et al.[13] studied the change in LVGLS after EVAR and showed a significant decrease in LVGLS values between baseline and the six-month follow-up, among patients who underwent EVAR. In the same study, no significant changes were observed in systolic blood pressure, diastolic blood pressure, or pulse pressure. The need for better prosthetic materials and improvement in endograft materials has been suggested for EVAR in previous articles.[25] However, the information about the implication of implantation of an endograft with TEVAR into the aorta is limited. Ghazy et al.[4] conducted a study that is analogous and correlative to ours, between 2009 and 2019, for which they evaluated ten patients who underwent TEVAR for blunt thoracic aortic trauma and a control group of ten healthy individuals, using cardiac magnetic resonance imaging (MRI). The study reported that in the TEVAR group, the 3D diastolic LV longitudinal strain ratio and velocities were significantly lower, compared to the control group. The authors attributed this result to the increased arterial stiffness, which primarily impairs the transmission of blood that should be delivered to the periphery during diastolic relaxation. This is, again, due to a reduction in the Windkessel function, leading to an increased afterload. However, their study was conducted using cardiac MRI: ours is distinctive in that it specifically examined LVGLS using echocardiography in patients who underwent TEVAR. Our results were consistent with those observed in research involving EVAR, however it is valuable to note that TEVAR involves the placement of endografts in the proximal portion of the aorta, while EVAR typically involves the implantation of endografts in the distal aorta. We hypothesize that the implantation of TEVAR grafts in the proximal aorta may have a more pronounced effect on the Windkessel effect, as this region plays a key role in the regulation of arterial compliance and afterload, potentially leading to greater alterations compared to EVAR.

Study Limitations

The patients' blood pressure measurements were performed as single office measurements, prior to the echocardiographic examination. Since LVGLS measurement is afterload-dependent, the decrease in LVGLS may not be directly associated with the impairment of LV systolic function. It would be more accurate to repeat the measurements after the patients became normotensive, or to reach a conclusion based on the average blood pressure obtained through 24-hour monitoring.

In the patients participating in the study, body surface area and body mass index were not evaluated, and it is known that these parameters have an effect on arterial blood pressure. Evaluating the changes in indexed aortic measurements according to these parameters, along with the decrease in LVGLS and arterial blood pressure, may provide us with a more comprehensive view of understand the possible hemodynamic effects of the TEVAR procedure.

Our study was a single-center observational study, and due to the limited sample size of eighteen patients, a detailed analysis of the TEVAR procedure could not be performed. Evaluations based on larger sample sizes, including factors such as procedure duration, the region of the aorta where the endograft is implanted, and the length of the endograft, may help us better understand the hemodynamic changes and remodeling process associated with TEVAR.

Conclusion

Our study suggests that implantation of an endograft to the proximal aorta via TEVAR procedure, may lead to increased stiffness and may implicate the afterload which affects LV functions. A decrease in LVGLS is a strong predictor of adverse cardiovascular outcomes, and based on the results of this study, we recommend that patients who undergo TEVAR should be closely monitored postoperatively with regular blood pressure checks and intermittent LVGLS measurements. This approach could facilitate the close monitoring of LV function and may help prevent cardiovascular mortality.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital (Approval Number: 2023.01-81, Date: 24.10.2023).

Informed Consent: Written informed consent was obtained from the patients.

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Evaluation of Left Atrial Function with Two-Dimensional Speckle Tracking Echocardiography in Patients Treated with Electrical Cardioversion and Catheter Ablation for Atrial Fibrillation

Atriyal Fibrilasyon İçin Elektriksel Kardiyoversiyon ve Kateter Ablasyonu ile Tedavi Edilen Hastalarda Sol Atriyal Fonksiyonun İki Boyutlu Speckle Tracking Ekokardiyografi ile Değerlendirilmesi

ABSTRACT

Objective: The effects of radiofrequency catheter ablation (RFCA) and direct current cardioversion (DCCV) on left atrial (LA) mechanical function and atrial myopathy are not fully understood. In this study, we aimed to compare the changes in myocardial deformation after catheter ablation and electrical cardioversion procedures, in patients with atrial fibrillation (AF).

Method: In this study, we retrospectively analyzed echocardiographic parameters of left ventricular and left atrial function and strain measurements with two-dimensional speckle tracking echocardiography (STE), before and after the procedure in patients who underwent RFCA or DCCV for atrial fibrillation.

Results: LA reservoir strain (LARS) significantly improved after the procedure in the ablation group (Apical four chamber view LARS 15.1 ± 8.2, 19.6 ± 7.1 P < 0.001, respectively). The Apical four chamber view LARS value also showed a significant improvement after the procedure, compared to the pre-procedure in patients who underwent DCCV (Apical four chamber view LARS 12.2 ± 6.2, 17.3 ± 8.1 P < 0.001, respectively). There was no significant difference in strain change between the groups (P = 0.7).

Conclusion: In our study, the improvement in the reservoir strain of patients who underwent RFCA was similar to DCCV group. These findings suggest that restoration of sinus rhythm by RFCA, despite the expense of fibrosis in the lesion areas, improves left atrial reservoir function.

Keywords: Atrial fibrillation, echocardiography, electrophysiology

ÖZET

Amaç: Radyofrekans kateter ablasyonu (RFKA) ve doğru akım kardiyoversiyon (DCCV) sol atriyal (LA) mekanik fonksiyon ve atriyal miyopati üzerindeki etkileri tam olarak anlaşılamamıştır. Bu çalışmada, atriyal fibrilasyonlu (AF) hastalarda kateter ablasyonu ve elektriksel kardiyoversiyon prosedürlerinden sonra miyokardiyal deformasyondaki değişiklikleri karşılaştırmayı amaçladık.

Yöntem: Bu çalışmada, atriyal fibrilasyon nedeniyle RFCA veya DCCV uygulanan hastalarda işlem öncesi ve sonrası sol ventrikül ve sol atriyal fonksiyon ekokardiyografik parametrelerini ve iki boyutlu benek takibi ekokardiyografi (BTE) ile strain ölçümlerini retrospektif olarak analiz ettik.

Bulgular: Ablasyon grubunda işlem öncesine kıyasla işlem sonrasında LA rezervuar strain (LARS) anlamlı olarak arttı (4 odacık LARS sırasıyla 15.1±8.2, 19.6±7.1 P < 0.001). DCCV uygulanan hastalarda da 4 odacıklı LARS değeri işlem öncesine kıyasla işlem sonrasında anlamlı bir iyileşme gösterdi (sırasıyla 4 odacıklı LARS 12,4±6,2, 17,3±8,1 P < 0,001). Gruplar arasında strain değişikliği açısından anlamlı bir fark yoktu (P = 0.7).

Sonuç: Çalışmamızda, RFKA uygulanan hastaların rezervuar gerinimindeki iyileşme DCCV grubuna benzerdi. Bu bulgular, lezyon alanlarında fibrozis pahasına da olsa, RFKA ile sinüs ritminin restorasyonunun sol atriyal rezervuar fonksiyonunu iyileştirdiğini göstermektedir.

Anahtar Kelimeler: Atriyal fibrilasyon, ekokardiyografi, elektrofizyoloji

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Atrial cardiomyopathy is a combination of structural, electrical, or functional changes in the atria leading to clinical effects and includes inflammatory and prothrombotic remodeling of the atria, neurohormonal activation, and fibrosis of myocardial tissue.[1] Atrial fibrillation (AF) itself causes atrial myopathy, which facilitates the long-term persistence of arrhythmia in the atrial myocardium, while atrial myopathy may contribute to the onset of AF.[2] The latest research indicates that treatments targeting the mechanism responsible for atrial myopathy may slow down the process of left atrial remodeling and facilitate reverse atrial remodeling.[3] The 2024 European Society of Cardiology (ESC) Guidelines for the management of atrial fibrillation, recommend rhythm-control strategy intended to improve AF-related symptoms and reduce morbidity and mortality in selected patient groups.[1,4–6]

Although there is evidence that radiofrequency catheter ablation (RFCA) improves left atrial (LA) function in patients with atrial fibrillation (AF), the procedure may also cause atrial damage by radiofrequency (RF) energy. While RFCA may enhance LA function by maintaining sinus rhythm, RFCA may also result in iatrogenic myocardial damage, leading to new scar formation and LA dysfunction.[7–9] There is also data in favour of improvement in atrial function and reverse remodeling after electrical cardioversion.[10]

So far, no study has compared changes in left atrial function after catheter ablation and electrical cardioversion. The primary aim of our study was to compare changes in myocardial deformation after radiofrequency catheter ablation and electrical cardioversion in patients with atrial fibrillation, as well as to determine how and to what extent these procedures affect the atrial reservoir function.

Materials and Methods

This cross-sectional study was conducted in accordance with the Declaration of Helsinki and received approval from Ankara University Human Research Ethics Committee (Approval Number: İ10-608-22, Date: 10.11.2022). Artificial intelligence-assisted technologies were not used in the production of this study.

Study Design and Patient Selection

In this study, we reviewed 660 patients who underwent catheter ablation or electrical cardioversion for atrial fibrillation at our center. Patients with appropriate images and measurements for strain by two-dimensional speckle tracking echocardiography in pre-procedural and post-procedural echocardiographic evaluations, were retrospectively screened. Patients with a left ventricular ejection fraction (LVEF) < 50%, a history of mechanical mitral valve replacement, mitral stenosis, or greater-than-moderate mitral regurgitation were excluded. In order to clearly evaluate the effect of sinus rhythm restoration, patients with AF recurrence within three months were excluded. Figure 1 shows the inclusion and exclusion flowchart for the study.

Echocardiographic Studies

Echocardiographic studies of the patients were obtained in the echocardiography laboratory of our hospital in accordance with the guidelines and recorded in the EchoPac system. The transthoracic echocardiogram (TTE) reports of the patients were retrospectively reviewed. The strain analyses were performed by a single cardiologist trained in advanced imaging and strain analysis. The cardiologist performing the follow-up speckle-tracking echocardiograms was unaware of the specific procedure applied to each patient. The GE Vivid E9 (GE Healthcare) was used as the echocardiography device and 2D speckle-tracking echocardiography measurements of LA strain and strain rate, were obtained according to the standardized measurement recommendations of the 2018 EACVI/ASE consensus document. If the LA image quality was not suitable for measurements or if tracking quality could not be improved by adjusting the region of interest (ROI), the image was not used to measure LA strain. Zero reference was defined as end-diastole. The analysis was performed using the Automated Function Imaging (AFI) method.

ABBREVIATIONS

A2C	Apical two chamber
A4C	Apical four chamber
AF	Atrial fibrillation
AFCARD	Acute kidney injury following cardioversion for atrial fibrillation
AFI	Automated function imaging
DCCV	Direct current cardioversion
ESC	European Society of Cardiology
LA	Left atrium
LAD	Left atrial diameter
LARS	Left atrial reservoir strain
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
RF	Radiofrequency
RFCA	Radiofrequency catheter ablation
ROI	Region of interest
SPAP	Systolic pulmonary artery pressure
STE	Speckle tracking echocardiography
TTE	Transthoracic echocardiogram

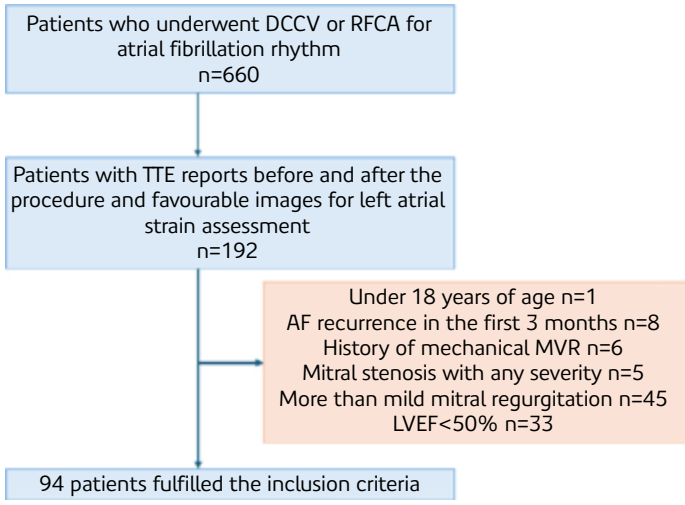

Figure 1. Patient inclusion flowchart for the study.

AF, Atrial fibrillation; DCCV, Direct current cardioversion; LVEF, Left ventricular ejection fraction; RFCA, Radiofrequency catheter ablation, TTE, Transthoracic echocardiogram.

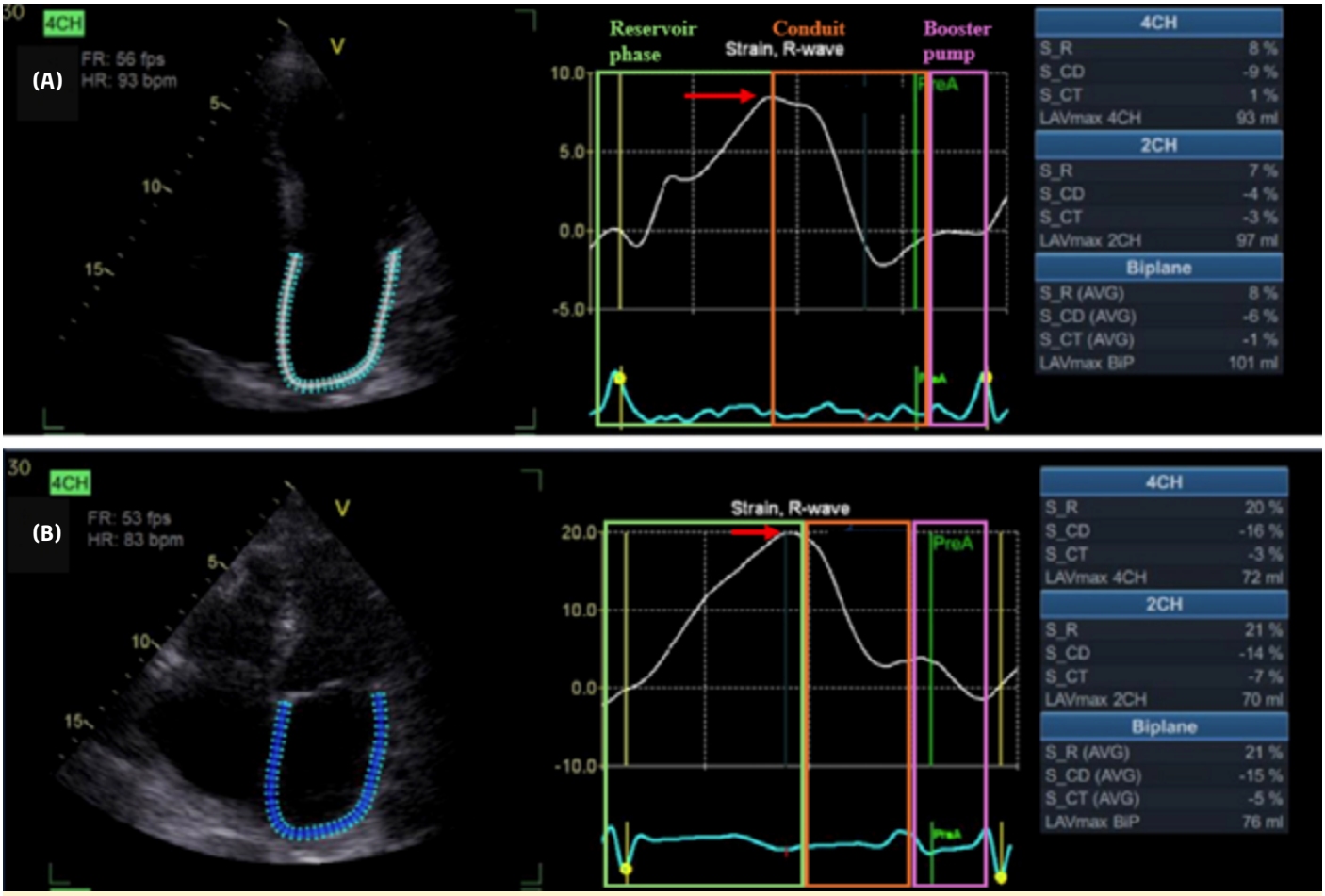

Figure 2. Pre-procedure (A) and post-procedure (B) measurements of LA reservoir strain by speckle tracking in a patient who underwent RFCA. Red arrows indicate A4C LARS values.

The LA reservoir strain (LARS) was calculated as LARS=peak systolic strain – the strain value at the end-diastole. LA diameter was measured from the parasternal long axis-view. LA strain analyses were performed with Automated Function Imaging (AFI) software. LA volumes at end-systole were determined from apical Two-Chamber (A2C) and apical Four-Chamber (A4C) view images, using the biplane area length method. Figure 2 shows LA strain measurements before and after the procedure in a patient evaluated with speckle-tracking echocardiography (STE). In patients with AF, an average of five beats was obtained in all measurements.

Clinical follow-up and Data Collection

Information on the demographic and clinical characteristics of all patients was obtained from the follow-up files and the hospital system. All patients underwent the clinical follow-up procedures that had been predetermined: they all underwent TTE before and three months after the procedure. Routine annual follow-up was planned unless the clinical condition required more frequent visits, and the echocardiographic images of the patients were retrospectively analyzed.

Ablation Procedure

In our clinic, a mapping catheter and an irrigated contact force sensing catheter were used for mapping and radiofrequency (RF) ablation. Navigation of the catheters was based on fluoroscopy and an electro-anatomical system (CARTO 3, Biosense Webster, Irwindale, CA, USA). The ipsilateral pulmonary veins were jointly isolated, and the maximum intersection distance was set to 6 mm. The endpoint of the procedure was the isolation of all pulmonary veins. Posterior wall isolation and scar homogenization or other procedures in addition to PVI were performed on an individual patient basis, at the initiative of the operator.

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics 23.0 software (IBM Corp., released in 2012, Armonk, NY, USA). Categorical variables were expressed as percentages and numerical variables were expressed as arithmetic means ± standard deviations. In addition to descriptive statistical methods (mean, standard deviation), independent t-tests were used in the comparison of independent groups and the Yates correction was used in the comparison of qualitative data. The Fisher's Exact test was used in case of the smallest theoretical frequency < 5. The paired t-test was used for the comparison of dependent variables. The results were considered statistically significant if the p-value was < 0.05.

Table 1. Comparison of demographic and clinical characteristics of patients treated with DCCV and RFCA

Variables	DCCV group (n = 45)	RFCA group (n = 49)	P
Age	65 ± 13	64.6 ± 12.1	0.9
Male sex, % (n)	49 (22)	49(24)	1
BSA	1.91 ± 0.18	1.92 ± 0.20	0.85
CHA2DS2VASc score	3.13 ± 1.6	2.9 ± 1.8	0.6
Persistent AF, % (n)	%83.2 (37)	%69.4 (34)	0.35
Paroxysmal AF, % (n)	%17.8 (8)	%30.6 (15)	0.30
Risk factors			
Hypertension, % (n)	%80 (36)	%70 (34)	0.34
Dyslipidemia, % (n)	%47 (21)	%43 (21)	0.84
Diabetes mellitus, % (n)	%27 (12)	%33 (16)	0.66
Smoking, % (n)	%24 (11)	%51 (25)	0.01
Stroke, %(n)	%2 (1)	%6 (3)	0.62
ASCVD, % (n)	%22 (10)	%31 (15)	0.48
Drugs			
ACEI, % (n)	%33 (15)	%27 (13)	0.5
ARB, % (n)	%40 (18)	%37 (18)	0.8
BB, % (n)	%75 (34)	%69 (34)	0.8
CCB, % (n)	%22 (10)	%14 (7)	0.42
Digitals, % (n)	%29 (13)	%8 (4)	0.01
Diuretic, % (n)	%40 (18)	%18 (9)	0.02
Statins, % (n)	%38 (17)	%39 (19)	1

AF, Atrial fibrillation; ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; ASCVD, Atherosclerotic cardiovascular disease; BB, Beta-blocker; BSA, Body surface area; CCB, Calcium channel blocker; DCCV, Direct current cardioversion.

Table 2. Comparison of pre-procedural echocardiographic parameters of patients with DCCV and RFCA

Echocardiographic parameters	DCCV group (n = 45)	RFCA group (n = 49)	P
LAD (mm)	46.18 ± 5.9	44.7 ± 8.2	0.31
LA area (mm^2)	22.7 ± 4.8	21.8 ± 5.7	0.54
LAVI (ml/m^2)	32.7 ± 11.01	31.9 ± 9.3	0.71
LAVmax (ml)	62.6 ± 20.4	62 ± 20.01	0.87
LVEDD (mm)	50.2 ± 5.96	49.3 ± 6.07	0.47
LVESD (mm)	33.8 ± 6.1	34.02 ± 7.5	0.86
LVEF (%)	58.2 ± 6.9	59.8 ± 6.3	0.26
TAPSE (cm)	2.27 ± 1.8	2.02 ± 0.33	0.38
SPAP (mmHg)	37.2 ± 12.8	38.2 ± 10.4	0.41
TRvmax (m/sn)	3.14 ± 3.1	2.6 ± 0.49	0.23
Mitral E (m/sn)	0.87 ± 0.25	0.78 ± 0.23	0.07
Mitral E/e' mean	10.2 ± 3.8	9.4 ± 2.85	0.34
A4C LARS (%)	12.4 ± 6.19	15.1 ± 8.2	0.81
Persistent AF	11.5 ± 5.3	12.2 ± 6.8	0.19
Paroxysmal AF	16.3 ± 8.4	21.5 ± 7.3	0.125

DCCV, Direct current cardioversion; LA, Left atrial; LAD, Left atrium diameter; LARS, Left atrial strain reservoir phase; LAVI, Left atrium volume index; LAVmax, Left atrium maximum volume; LVEDD, Left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; LVESD, Left ventricular end-systolic diameter; RFCA, Radiofrequency catheter ablation; SPAP, Systolic pulmonary artery pressure; TAPSE, Tricuspid annular plane systolic motion.

Results

Patient Characteristics

Our study was performed with 45 patients who underwent electrical cardioversion (DCCV) and 49 patients who underwent radiofrequency catheter ablation (RFCA). The rate of smoking was significantly higher in patients who underwent RFCA. The groups were similar in terms of age, gender, presence of atherosclerotic heart disease, hypertension, dyslipidemias and diabetes. There was no significant difference in the type of atrial fibrillation between the DCCV and RFCA groups. All patients in the study were in sinus rhythm at three months and patients with AF recurrence were not included in the study. AF recurrence is a critical outcome that affects LA function and remodeling, and patients with AF recurrence were not included in our study to ensure homogeneity of the groups and because the LARS value may be influenced by the current rhythm.

Detailed information about the descriptive characteristics of the patients is presented in Table 1.

When pre-procedural echocardiographic parameters were evaluated, the LA area was 22.7 ± 4.8 mm^2 in the DCCV group and 21.8 ± 5.7 mm^2 in the RFCA group and no significant difference was found (P = 0.54). LAVI was 32.7 ± 11.01 (ml/m^2) in the DCCV group and 31.9 ± 9.3 (ml/m^2) in the RFCA group and no difference was found between the groups (P = 0.71). When the pre-procedure two-dimensional STE measurements of the patients were compared, no statistically significant difference was observed in strain parameters. A4C LARS was 12.43 ± 6.19% in the DCCV group and 15.1 ± 8.2% in the RFCA group (P = 0.81). A4C LARS values were found to be higher in the RFCA group before the procedure, but no statistically significant difference was found. Pre-procedural echocardiographic parameters are shown in Table 2.

When the pre-procedural and three-month post-procedural control echocardiographic findings of all patients were compared, the post-procedural decrease in left atrium diameter (LAD) was found to be statistically significant. The mean values of SPAP and Mitral E/e' were significantly lower after the procedure. A4C LARS was found to be significantly increased after the procedure. When the echocardiographic parameters of the RFCA group were evaluated before and after the procedure, it was found that although there was a decrease in LAVI, it did not reach statistical significance, but there was a statistically significant decrease in LAVmax and SPAP. A4C LARS was found to be significantly higher after the procedure (P < 0.001). The results demonstrated no notable alteration in LAVI, LAVmax and LA area, in patients who underwent electrical cardioversion. The mean mitral E/e' value in mitral flow samples of the patients was significantly lower after the procedure. Furthermore, A4C LARS was found to be significantly higher after the procedure (P < 0.001). Details regarding the comparison of echocardiographic parameters of all patients and groups before and after the procedure are provided in

Table 3. Comparison of echocardiographic parameters of patients before and after the procedure

	All patients (n = 94)			RFCA group			DCCV group		
	Pre-procedural measurements	Post-procedural measurements	P	Pre-procedural measurements	Post-procedural measurements	P	Pre-procedural measurements	Post-procedural measurements	P
LAD (mm)	45.4 ± 7.3	43 ± 10	0.03	44.73 ± 8.3	41.1 ± 12.2	0.08	46.3 ± 6	45.1 ± 6.7	0.02
LA area (mm^2)	23.8 ± 14.5	21.6 ± 5.4	0.14	21,8 ± 5,7	20.8 ± 5.4	0.2	22.8 ± 4.8	22.4 ± 5.3	0.6
LAVI (ml/m^2)	32.4 ± 10.2	31.4 ± 10.2	0.12	32.1 ± 9.4	30.4 ± 9.5	0.07	32.7 ± 11.1	32.5 ± 10.9	0.8
LAVmax (ml)	62.4 ± 20.3	60.4 ± 20.2	0.1	62.6 ± 20.2	58.7 ± 20.1	0.03	62.6 ± 20.6	62.3 ± 20.6	0.9
LVEDD (mm)	49.8 ± 6.1	49.2 ± 7.7	0.4	49.3 ± 6.1	48.3 ± 8.8	0.4	50.3 ± 6	50.2 ± 6.1	0.9
LVESD (mm)	33.9 ± 6.9	33.7 ± 7.6	0.85	33.9 ± 7.5	33.3 ± 7.8	0.6	33.8 ± 6.2	34.2 ± 7.5	0.6
LVEF (%)	58.7 ± 6.6	59,29 ± 5,93	0.44	59.3 ± 6.1	60.2 ± 5.2	0.14	57.8 ± 7	58,7 ± 5,22	0.4
TAPSE (cm)	2.2 ± 1.3	2.04 ± 0.33	0.5	2.0 ± 0.3	2.1 ± 0.3	0.2	2.3 ± 1.9	2.0 ± 0.4	0.4
SPAP (mmHg)	2.88 ± 2.3	2.6 ± 0.47	0.23	2.6 ± 0.5	2.5 ± 0.5	0.3	3.2 ± 3.3	2.6 ± 0.5	0.3
TRvmax (m/sn)	36.4 ± 12	33.6 ± 10.2	0.007	35.2 ± 10.7	31.8 ± 10	0.03	37.8 ± 13.3	36 ± 10	0.2
Mitral E (m/sn)	0.80 ± 0.23	0.79 ± 0.22	0.24	0.8 ± 0.21	0.8 ± 0.2	0.8	0.84 ± 0.24	0.81 ± 0.22	0.1
Mitral E/e' mean	10.2 ± 3.3	9.3 ± 3.24	0.01	9.7 ± 2.5	8.8 ± 2.8	0.08	10.7 ± 3.9	9.6 ± 3.7	0.002
A4C LARS (%)	13.7 ± 7.29	18.5 ± 7.7	<0.001	15.1 ± 8.2	19.6 ± 7.3	<0.001	12.4 ± 5.8	17.3 ± 8.1	<0.001

A4C, Apical four chamber; DCCV, Direct current cardioversion; LAD, Left atrium diameter; LARS, Left atrial strain reservoir phase; LAVI, Left atrium volume index; LAVmax, Left atrium maximum volume; LVEDD, Left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; LVESD, Left ventricular end-systolic diameter; RFCA, Radiofrequency catheter ablation; SPAP, Systolic pulmonary artery pressure; TAPSE, Tricuspid annular plane systolic motion.

Table 4. Pre and postprocedural A4C LARS values of patients according to atrial fibrillation types

	Persistent AF	Paroxysmal AF	P
Preprocedural A4C LARS	11.8 ± 6.2	19.7 ± 7.9	<0.001
DCCV	11.5 ± 5.3	16.3 ± 8.4	0.001
RFCA	12.2 ± 6.8	21.5 ± 7.3	<0.001
Postprocedural A4C LARS	16.8 ± 6.0	23.6 ± 7.4	<0.001
DCCV	16.0 ± 7.8	22.7 ± 7.0	0.03
RFCA	12.2 ± 6.8	24.1 ± 5.9	<0.003

AF, Atrial fibrillation; DCCV, electrical cardioversion; LARS, Left atrial strain reservoir phase; RFCA, radiofrequency catheter ablation.

Figure 3. Change in the A4C LARS value of the groups before and after the procedure..

DCCV, Direct current cardioversion; RFCA, Radiofrequency catheter ablation.

Table 3. Pre- and post-procedure A4C LARS values of all patients, the RFCA group and the DCCV group are summarized in Figure 3.

Table 4 shows the A4C LARS values according to the atrial fibrillation subgroups of patients and the procedure performed. The LARS value of patients with persistent AF was lower than that of patients with paroxysmal AF in both groups before and after the procedure. However, both procedures were associated with an improvement in reservoir function in both the paroxysmal and persistent AF patient subgroups.

The A4C LARS in the DCCV group was 12.4 ± 6.2% and 17.3 ± 8.1% before and after the procedure, respectively, and in the RFCA group it was 15.1 ± 8.2% and 19.6 ± 7.1%, respectively, and no significant difference was found between the groups in terms of LARS increase (P = 0.4). Similarly, the change in other echocardiographic findings was similar between the two groups. Detailed information about the evaluation of the changes in echocardiographic parameters in patients who underwent DCCV and RFCA is given in Table 5.

One of the patients presented with dyspnea and pulmonary edema within 48 hours of AF ablation. Pre-procedural echocardiography showed moderate mitral regurgitation, moderate to severe tricuspid regurgitation and stage 2 diastolic dysfunction. The A4C LARS was 8% pre-procedure and 10% post-procedure. The patient's left atrial mapping showed diffuse low-voltage areas and posterior wall isolation was performed in addition to PVI. We suspected that the patient had developed stiff atrium syndrome. One of our patients who underwent cardioversion developed acute kidney injury following cardioversion for atrial fibrillation (AFCARD)

Table 5. Comparison of the change in baseline and 3rd month measurements of patients

Groups and variables		Pre-procedural measurements	Post-procedural measurements	P
DCCV	LAD (mm)	46.3 ± 6.0	45.1 ± 6.7	0.33
RFCA		44.6 ± 8.2	41.1 ± 12.1	
DCCV	LA area (mm^2)	22.8 ± 4.8	22.4 ± 5.3	0.3
RFCA		21,8 ± 5,7	20.8 ± 5.4	
DCCV	LAVI (ml/m^2)	32.7 ± 11.1	32.5 ± 10.9	0.7
RFCA		32 ± 9.3	30.4 ± 9.5	
DCCV	LAVmax (ml/m^2)	62.6 ± 20.6	62.3 ± 20.6	0.6
RFCA		62 ± 20	58.6 ± 20	
DCCV	LVEDD (mm)	50.3 ± 6	50.2 ± 6.12	0.62
RFCA		49.3 ± 6.06	48.3 ± 8.8	
DCCV	LVESD (mm)	33.8 ± 6.2	34.2 ± 7.5	0.6
RFCA		34 ± 7.5	33.3 ± 7.8	
DCCV	LVEF (%)	57.8 ± 7	72 ± 84.6	0.3
RFCA		59.3 ± 6.2	60.3 ± 5.2	
DCCV	TAPSE (cm)	2.3 ± 1.9	2.01 ± 0.4	0.3
RFCA		2.0 ± 0.33	2.1 ± 0.3	
DCCV	TRvmax (m/sn)	3.2 ± 3.3	2.6 ± 0.5	0.7
RFCA		2.6 ± 0.5	2.5 ± 0.5	
DCCV	SPAP (mmHg)	37.8 ± 13.3	36.2 ± 10	0.58
RFCA		35.2 ± 10.7	31.8 ± 10	
DCCV	Mitral E (m/sn)	0.84 ± 0.24	0.80 ± 0.22	0.32
RFCA		0.8 ± 0.21	0.8 ± 0.23	
DCCV	Mitral E/e' mean	10.7 ± 3.8	9.6 ± 3.7	0.9
RFCA		9.7 ± 2.5	8.8 ± 3	
DCCV	A4C LARS (%)	12.4 ± 6.2	17.3 ± 8.1	0.4
RFCA		15.1 ± 8.2	19.6 ± 7.1	

A4C, Apical four chamber; DCCV, Direct current cardioversion, LA, Left atrial; LAD, Left atrium diameter; LAVI, Left atrium volume index; LAVmax, Left atrium maximum volume; LARS, Left atrial strain reservoir phase; LVEDD, Left ventricular end-diastolic diameter; LVESD, Left ventricular end-systolic diameter; LVEF, Left ventricular ejection fraction.

syndrome. The 82-year-old male patient was in New York Heart Association (NYHA) class II before the procedure. He had a known diagnosis of heart failure with preserved ejection fraction (EF). Pre-procedural echocardiogram showed grade 2 diastolic dysfunction, dilated left atrium, moderate mitral regurgitation, moderate tricuspid regurgitation (thought to be functional), dilated IVC and elevated pulmonary artery systolic pressure (SPAP: 55 mmHg). On the day after cardioversion, the patient had elevated serum creatinine, dyspnea and a nasal O2 requirement of 4 L/min. The patient's creatinine level was 1.61 mg/dL pre-procedure and increased to 3.10 mg/dL post-procedure. In the ablation group, a femoral hematoma was noted in four patients and a pseudoaneurysm requiring surgical repair in one patient.

Discussion

In our study, we observed improvement in left atrial reservoir function in patients with atrial fibrillation who achieved sinus rhythm with RFCA and DCCV. Our study contributes to the literature in this context by suggesting that rhythm control strategies may promote atrial reverse remodeling.

The reservoir, conduit and booster pump functions of the LA can be quantitatively assessed by speckle tracking echocardiography of the left atrium. LA strain is sensitive to subtle changes and can detect changes in LA myocardial function before macroscopic changes are observed.[11,12] Recent studies have shown that LA reservoir strain is a strong and sensitive marker for the development of AF and that a decrease in LA strain is a marker of fibrotic atrium with reduced contractile capacity and decreased compliance.[13–15] In our study, we used left atrial reservoir strain assessment as a marker of changes in left atrial mechanical function, after sinus rhythm restoration by catheter ablation and electrical cardioversion.

The A4C LARS values of patients who underwent DCCV and RFCA increased three months after the procedure compared to the pre-procedure values. The increase in left atrial reservoir strain observed in this study may be associated with atrial reverse remodeling. In a study that examined biatrial remodeling in patients with AF who had undergone successful electrical cardioversion, a notable reduction in LA 3D volumes and a substantial enhancement in left atrial strain were

observed six months after the procedure. They published that cardioversion has potential favorable effects on LA functional remodeling.[10]

The effects of catheter ablation on left atrial mechanical function remain unclear. One study demonstrated a decline in left atrial function immediately following catheter ablation.[16] In some previous studies, thermal methods such as RF were found to cause coagulation necrosis, including edema, intramural hemorrhage and microvascular damage. In the chronic phase, these lesions are thought to transform into areas of reparative fibrosis, leading to increased scar tissue and decreased compliance after ablation. Cochet et al.[17] published a study supporting an increase in post-procedural scar burden and a decrease in reservoir function in patients evaluated with cardiac magnetic resonance imaging (MRI). Nakatani et al.[18] compared pulsed field ablation and catheter ablation and found that acute late gadolinium enhancement (LGE) involvement evaluated by cardiac MRI improved in patients undergoing pulsed field ablation, but acute LGE involvement persisted in most patients undergoing thermal RF ablation. Another recent study performed cardiac MRI and echocardiographic LA strain assessment and found that the decrease in LA mechanical function after ablation recovered approximately ten days after ablation.[19] In our study, we aimed to compare whether there was a difference in the change in atrial function in patients who underwent RFCA or DCCV. The recovery of reservoir strain in the RFCA group was similar to the DCCV group. There are concerns that there may be a decrease in diastolic function and/or compliance of the LA after radiofrequency ablation of AF. Stiff LA syndrome after catheter ablation for AF is a potential complication of the procedure. Loss of cardiomyocytes after catheter ablation has been shown to cause replacement fibrosis affecting up to 30-35% of the LA wall. While this may be moderate and well tolerated in patients with paroxysmal AF and a healthy atrium, patients with a fibrotic left atrium with reduced compliance, especially those with HFpEF, are at higher risk of stiff LA syndrome.[20–22]

Limitations of the Study

Our study was retrospective and included patients who had echocardiographic measurements three months after the procedure and fulfilled the eligibility criteria for evaluation by speckle-tracking echocardiography. Patients with insufficient image quality to measure LA strain were excluded from the study, which may have lead to selection bias. The number of patients who underwent catheter ablation or cardioversion for atrial fibrillation in our clinic is much higher than the study group. The effect of RFCA and DCCV on LA structure and function needs to be confirmed in larger, randomized controlled trials. Another important limitation is that the most reliable LARS measurements can be performed under sinus rhythm, however, all of our cardioversion patients and the majority of patients in the ablation group were in AF rhythm, before the procedure. It is difficult to determine whether the changes in left atrial reservoir strain three months after the procedure are due to changes in cardiac rhythm or to the actual remodeling process. Follow-up at three months is probably too short to fully assess cardiac remodeling.

Conclusion

The present study demonstrates that the improvement in reservoir strain observed in patients who underwent radiofrequency catheter ablation, is comparable to that observed in the electrical cardioversion group. These findings suggest that restoration of sinus rhythm leads to an improvement in left atrial reservoir function despite fibrosis in the lesion areas in patients who have undergone RFCA.

Ethics Committee Approval: Ethics committee approval was obtained from Ankara University Human Research Ethics Committee (Approval Number: İ10-608-22, Date: 10.11.2022).

Informed Consent: Written informed consent was not required due to the retrospective nature of the study.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Use of AI for Writing Assistance: Artificial intelligence-assisted technologies were not used in the production of this study.

Author Contributions: Concept – B.K.G., İ.D.; Design – İ.D., T.S.T.; Supervision – İ.D., E.B.; Resource – B.K.G., T.S.T.; Data Collection and/or Processing - B.K.G., E.B.; Analysis and/or Interpretation - B.K.G., T.S.T.; Literature Review – B.K.G.; Writing – B.K.G., İ.D.; Critical Review – İ.D., T.S.T.

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Local Anesthetic-Related Methemoglobinemia During Cardiac Device Implantation; A Retrospective Registry: The LAMDA Study

Kardiyak Cihaz İmplantasyonu Sırasında Lokal Anesteziye Bağlı Methemoglobinemi; Retrospektif Bir Kayıt: LAMDA Çalışması

ABSTRACT

Objective: This study aimed to determine the frequency of methemoglobin development and identify associated factors in patients undergoing Implantable Cardioverter-Defibrillator (ICD) and Cardiac Resynchronization Therapy (CRT) procedures, with the local anesthetic prilocaine.

Method: The data from 64 patients was analyzed. The patients' methemoglobin levels before and after the procedure were measured and compared. The relationships between the results and factors such as creatinine, hemoglobin, body mass index (BMI) the incidence was not effected and the amount of prilocaine used were examined. Exclusion criteria included being aged under 18 years, pregnant, breastfeeding, presence of malignancy, undergoing chemotherapy, hemoglobin chain disorders, liver failure and renal failure (glomerular filtration rate (GFR) < 60 ml/min), chronic obstructive pulmonary disease, other hypoxic lung diseases and being a smoker.

Results: Methemoglobin levels were significantly higher in the first hour after the procedure ($P < 0.001$). Oxygen saturation levels were significantly lower during the first hour post-procedure ($P < 0.001$). In the group with elevated methemoglobin levels after the procedure, creatinine levels were significantly higher ($P < 0.001$), while BMI ($P < 0.001$) and hemoglobin levels ($P < 0.001$) were significantly lower. No significant relationship was found with alanine transaminase (ALT) levels ($P = 0.425$).

Conclusion: While significant methemoglobin elevation was observed following ICD/CRT procedures with prilocaine, clinically significant methemoglobinemia cases are rare. A significant relationship was identified between methemoglobin elevation and BMI, hemoglobin and creatinine.

Keywords: Cardiac resynchronization therapy, implantable cardioverter-defibrillator, methemoglobin, methemoglobinemia, prilocaine

ÖZET

Amaç: Bu çalışma, lokal anestezik prilokain ile Implantable Cardioverter-Defibrillator (ICD) ve Cardiac Resynchronization Therapy (CRT) prosedürleri uygulanan hastalarda methemoglobin gelişme sıklığını belirlemeyi ve ilişkili faktörleri tanımlamayı amaçlamıştır.

Yöntem: 64 hastanın verileri analiz edilmiştir. Hastaların işlem öncesi ve sonrası methemoglobin seviyeleri ölçülmüş ve karşılaştırılmıştır. Elde edilen sonuçlarla kreatinin, hemoglobin, BMI ve kullanılan prilokain miktarı gibi faktörler arasındaki ilişkiler incelenmiştir. Çalışmaya dahil edilmeyen kriterler: 18 yaş altı, hamilelik, emzirme, malignite, kemoterapi, hemoglobin zincir hastalıkları, karaciğer yetmezliği ve böbrek yetmezliği (GFR < 60 ml/dak), kronik obstrüktif akciğer hastalığı, diğer hipoksik akciğer hastalıkları ve sigara içen hastalar idi.

Bulgular: İşlem sonrası ilk saatte methemoglobin seviyeleri anlamlı şekilde yüksek bulunmuştur ($P < 0.001$). Oksijen saturasyonu seviyeleri ise işlem sonrası ilk saatte anlamlı şekilde düşük olmuştur ($P < 0.001$). Prosedür sonrası yükselmiş methemoglobin seviyelerine sahip olan grupta, kreatinin seviyeleri anlamlı şekilde yüksek ($P < 0.001$), BMI ($P < 0.001$) ve hemoglobin seviyeleri ise anlamlı şekilde düşük bulunmuştur ($P < 0.001$). ALT seviyeleri ile anlamlı bir ilişki bulunmamıştır ($P = 0.425$).

Sonuç: Prilokain ile gerçekleştirilen ICD/CRT prosedürlerinden sonra önemli methemoglobin yükselmesi gözlemlense de, klinik olarak anlamlı methemoglobinemia vakaları nadirdir. Methemoglobin yükselmesi ile BMI, hemoglobin ve kreatinin arasında anlamlı bir ilişki bulunmuştur.

Anahtar Kelimeler: Kardiyak resenkronizasyon tedavisi, implante edilebilir kardiyoverter-defibrilatör, methemoglobin, methemoglobinemi, prilokain

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Methemoglobinemia, though rare, can be life-threatening if unrecognized.[1] In healthy individuals, the iron in hemoglobin (Hb) remains in the divalent form (Fe^{2+}) to facilitate oxygen binding and delivery. In contrast, methemoglobin (MetHb) contains iron in the trivalent form (Fe^{3+}), which reduces oxygen affinity and impairs binding.[2] Typically, 2–3% of hemoglobin is converted to methemoglobin, but this is kept below 1% through metabolic pathways.[3] Disruption of these pathways leads to elevated MetHb levels. A key clinical sign of methemoglobinemia is blue-gray cyanosis unresponsive to oxygen therapy, although other symptoms, such as cough, dizziness, shortness of breath, dysrhythmias, confusion, circulatory issues and even death, may also occur.[4] Methemoglobinemia can be hereditary or acquired, with the latter being more common. Various drugs and chemicals, including nitrites, nitrates and chlorates, have been implicated in causing this condition.[5]

Local anesthetics are commonly used in cardiovascular procedures such as coronary angiography, transesophageal echocardiography and permanent pacemaker implantation. While methemoglobinemia is rare with local anesthetics, its toxicity can be severe and potentially fatal, necessitating careful monitoring post-procedure. This study aimed to investigate methemoglobinemia and related factors in patients receiving Implantable Cardioverter-Defibrillator (ICD) and Cardiac Resynchronization Therapy (CRT) devices, with local anesthetics.

Methods

Ethical Considerations

The study was approved by the Kütahya Health Sciences University Rectorate Non-Interventional Clinical Research Ethics Committee (Approval Number: 2021/40, Date: 05.03.2021) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study Design

This retrospective study aimed to investigate methemoglobinemia occurring in the postoperative period due to local anesthetic administration, during ICD and CRT device implantation. The study was conducted at a tertiary facility specializing in advanced cardiovascular care. No artificial intelligence-supported technologies were used in the study.

Study Population

Patients who received ICD and CRT devices were included in the study.

Inclusion criteria:

- Age ≥ 18 years
- Voluntary participation

Exclusion criteria:

- Age < 18 years
- Pregnancy
- Active lactation
- Active malignancy or ongoing chemotherapy
- Hemoglobin chain disorders

ABBREVIATIONS

ALT	Alanine transaminase
BMI	Body mass index
CRT	Cardiac resynchronization therapy
FDA	Food and drug administration
GFR	Glomerular filtration rate
Hb	Hemoglobin
ICD	Implantable cardioverter-defibrillator
MetHb	Methemoglobin
TEE	Transesophageal echocardiography

- Liver failure
- Renal failure with glomerular filtration rate (GFR) < 60 mL/min or dialysis treatment
- Chronic obstructive pulmonary disease and other hypoxic lung diseases (eg: Interstitial lung diseases, asthma, occupational diseases)
- Smokers
- Use of other sedative agents

Data Collection and Measurements

Patient data were obtained from the hospital's electronic medical records. Demographic parameters (age, sex, weight, height) were recorded. Body mass index (BMI) was calculated as weight (kg) / height^2 (m^2). Laboratory values, including urea, creatinine, alanine aminotransferase (ALT) and hemoglobin levels, were extracted from the clinical database. Patients with missing data were excluded from the study. No additional procedures were performed; all patients were monitored observationally. Pre-procedural laboratory data were recorded and compared with values obtained one-hour post-procedure. The amount of prilocaine administered was also documented.

Outcomes

The primary outcome was the change in methemoglobin levels post-procedure. Secondary outcomes included identifying factors associated with this change, assessing the impact of methemoglobin levels on oxygen saturation and determining the factors influencing changes in oxygen saturation.

Statistical Analysis

Normality was assessed using the Shapiro-Wilk test. Continuous variables are presented as means±standard deviation (SD) for normally distributed data and as medians (minimum-maximum) for non-normally distributed data. Categorical variables are presented as frequencies and percentages. The Spearman correlation test was used for continuous variables, while the Mann-Whitney U test was applied to compare non-normally distributed variables. The Wilcoxon test was used for dependent variables. A P-value < 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS (version 26.0, IBM Corp., Armonk, NY, USA).

Results

A total of 64 patients were included in the study, consisting of 35 males (54.7%) and 29 females (45.3%), with a mean age of 57.02 ± 6.53 years (Table 1). The average weight of the patients

Table 1. Demographic, anthropometric and clinical data of the study population (n=64)

	Min	Max	Mean	SD
Age (years)	38	69	57.02	6.53
Weight (kg)	50	93	71.41	11.08
Height (cm)	155	180	166.09	8.17
BMI (kg/m^2)	18.37	30.37	25.7	2.82

SD, Standard deviation; BMI, Body mass index.

was 71.41 ± 11.08 kg, the mean height was 166.09 ± 8.17 cm and the average BMI was 25.7 ± 2.82 (Table 1). No significant relationship was found between age and methemoglobin levels (P = 0.059). However, significant associations were observed between elevated methemoglobin levels and both weight (P < 0.001) and BMI (P < 0.001) (Table 2). No significant relationship was found between height and methemoglobin levels (P = 0.611) (Table 2).

Laboratory tests revealed a significant relationship between creatinine levels and methemoglobin levels (P < 0.001) (Table 2), as well as a positive correlation between changes in methemoglobin and creatinine levels (P < 0.001) (Table 3). Additionally, a positive correlation was found between changes in oxygen saturation and methemoglobin levels (P = 0.009) (Table 3). No significant relationship was observed between ALT levels and methemoglobinemia (P = 0.425) (Table 2). Total prilocaine doses greater than 600 mg were used in 51 patients and only one patient developed clinically significant methemoglobinemia.

Prilocaine administration was significantly associated with higher methemoglobin levels (P < 0.001) and lower oxygen saturation (P < 0.001) (Table 2). The amount of prilocaine administered showed a positive correlation with both methemoglobin levels (P = 0.006) and changes in oxygen saturation (P = 0.007) (Table 3).

In our study, post-procedural methemoglobin levels were found to be significantly higher compared to pre-procedural values (P < 0.001), while oxygen exchange was significantly lower (P < 0.001) (Table 4). In the regression analysis, the risk of methemoglobin was found to be high when BMI was low (odds ratio (OR): 6.8), hemoglobin was low (OR: 9.9) and the mg of prilocaine used increased (OR: 0.99). In the multiple regression analysis, low BMI (OR: 5.2) among the variables increased the risk of methemoglobinemia (Table 5).

Discussion

Our study is among the first to investigate the development of methemoglobinemia in patients undergoing ICD and CRT procedures under prilocaine anesthesia and to explore the factors contributing to this condition. The indications and technologies for pacemaker implantation are continuously evolving and these procedures are generally regarded as minor surgeries. Consequently, local anesthesia is the preferred method for performing these procedures.[6] Prilocaine is often the preferred agent in the procedures performed and according to the advice of the US Food and Drug Administration (FDA) the maximum safe dose of prilocaine in normal and healthy individuals is 600 mg. Although these procedures are typically safe, complications can occasionally arise. These include pneumothorax, hemothorax, hematoma, pacemaker system infection, diaphragm stimulation and cardiac or venous perforation. However, methemoglobinemia—a rare complication—occurs infrequently.

Cases of methemoglobinemia induced by prilocaine, a local anesthetic used during pacemaker implantation, are scarce in the literature. Methemoglobin levels increase when oxidative stress within red blood cells overwhelms their mechanisms. This stress causes the iron ion in the heme group (Fe^{2+}) to oxidize to the ferric state (Fe^{3+}), resulting in methemoglobin (MetHb), which is incapable of binding oxygen effectively. Normally, MetHb levels remain below 2%, not causing symptoms. However, these levels can rise due to genetic factors (e.g., enzymatic defects) and/or acquired causes (e.g., drugs, toxins).[7,8] Elevated methemoglobin concentrations often lead to more pronounced symptoms. The metabolic mechanisms

Table 2. Methemoglobinemia and associated factors

	Methemoglobin value < 10 (%)		Methemoglobin value > 10 (%)		p
	Mean ± SD	Median (Min–Max)	Mean ± SD	Median (Min–Max)	
Age (years)	56.54±6.0	56 (44–67)	59.6±8.6	60 (38–69)	0.059
Height (cm)	166.2 ± 8.5	170 (155–180)	165.2 ± 6.2	166 (155–175)	0.611
Weight (kg)	73.9 ± 9.7	76 (50–93)	57.5 ± 6.8	58 (50–68)	**<0.001**
BMI (kg/m^2)	26.6 ± 2.0	27 (20.8–30.3)	21.0 ± 1.3	21.4 (18.3–22.4)	**<0.001**
Delta oxygen saturation	0.66±0.86	1.0 (–1.0–3.0)	3.8±3.6	3.0 (2.0–14.0)	**<0.001**
Total prilocation dose (mg)	728.5 ± 136.6	700 (500–1200)	836.0±60.2	800 (800–960)	**<0.001**
ALT (U/L)	22.1±5.2	21.5 (14–33)	23.4±5.3	25 (12–31)	0.425
Serum creatinine (mg/dl)	0.85±0.11	0.86 (0.60–1.16)	1.18±0.15	1.1 (0.97–1.40)	**<0.001**
Urea (mg/dl)	22±4.7	22 (14–37)	31.6±7.7	32.5 (19–43)	**<0.001**
Hgb (g/dL)	12.8 ± 1.2	12.7 (9.6–15.8)	10.4 ± 0.6	10.4 (9.5–11.4)	**<0.001**

*Mann-Whitney U test; ALT, Alanin amino transferaz; BMI, Body mass index; Hgb, Hemoglobin; SD, Standard deviation.

Table 3. Correlation test of delta methemoglobin and delta oxygen saturation related factors

	Delta methemoglobin		Delta oxygen saturation	
	Factor (rho)	**P**	**Factor (rho)**	**P**
Delta methemoglobin (%)	–	–	0.825	**<0.001**
Delta oxygen saturation	0.825	**<0.001**	–	–
Age (years)	0.046	0.774	-0.185	0.144
BMI (kg/m^2)	-0.642	**<0.001**	-0.388	**0.002**
Total prilocation dose (mg)	0.337	**0.006**	0.337	**0.007**
Prilocaine (mg/kg)	0.617	**<0.001**	0.412	**<0.001**
ALT (U/L)	0.099	0.435	0.066	0.606
Serum creatinine (mg/dl)	0.607	**<0.001**	0.323	**0.009**
Urea (mg/dl)	0.471	**<0.001**	0.260	**0.038**
Hgb (g/dl)	-0.612	**<0.001**	-0.359	**0.004**

*Spearman Correlation Test; ALT, Alanin amino transferaz; BMI, Body mass index; Hgb, Hemoglobin; SD, Standard deviation.

Table 4. Changes in pre- and post-operative parameters

	Before operation		After operation		P
	Mean ± SD	**Min–Max**	**Mean ± SD**	**Min–Max**	
Methemoglobin (%)	0.82±0.138	0.6–1.2	6.2±3.8	2.7–25.1	**<0.001**
Oxygen saturation (So_2)	97±1.0	94–98	95.8±2.1	84–98	**<0.001**

*Wilcoxon test; SD, Standard deviation.

Table 5. Effect of independent variables on methemoglobin change (logistic regression analysis)

	Model 1					Model 2			
	OR	**95% CI**		**P**		**OR**	**95% CI**		**P**
BMI (kg/m^2)	6.8	1.5	31.1	**0.012**	-	5.2	1.0	25.3	**0.04**
Hemoglobin(g/dl)	9.9	2.7	36.7	**<0.001**					
Total prilocation dose (mg)	0.99	0.98	0.99	**0.03**					

CI, Confidence interval; OR, Odd ratios; BMI, Body mass index.

counteracting MetHb primarily involve cytochrome b5 reductase and NADPH meth-Hb reductase enzyme systems in red blood cells, with lesser contributions from ascorbic acid and glutathione enzyme systems. Disruption of these pathways can result in methemoglobinemia.[9]

Guay[10] reported a review of 242 methemoglobinemia cases linked to local anesthesia. Of these, 159 (65.7%) patients were anesthetized with benzocaine-containing agents, with 105 (43.4%) receiving benzocaine alone and twelve cases of methemoglobinemia were associated with lidocaine administration.[10] In another study of 24,431 patients undergoing endoscopic procedures, no cases of methemoglobinemia occurred in 22,210 patients anesthetized with 4% lidocaine spray for upper gastrointestinal endoscopy or bronchoscopy. In contrast, in the second group of 2,221 patients who received 20% benzocaine spray prior to transesophageal echocardiography (TEE), nine cases of clinically significant methemoglobinemia were reported.[11] Strzecka DF examined data from 3,354 patients over a 13-year period and reported no cases of methemoglobinemia requiring clinical intervention in anesthesia performed with lidocaine.[12]

Cases of methemoglobinemia related to prilocaine are less common. Cicek et al.[13] reported a case where a patient undergoing an ICD procedure developed low oxygen saturation post-procedure, with high methemoglobin levels detected. Following treatment with methylene blue, methemoglobin levels decreased and the patient's vital signs improved. Similarly, Canpolat et al.[9] described a case where methemoglobinemia developed following prilocaine administration during an ICD procedure.

Our study is pioneering in investigating methemoglobinemia specifically in the context of ICD/CRT procedures under prilocaine anesthesia. The results of our study show a statistically significant increase in methemoglobin levels following prilocaine administration. Furthermore, significant decreases in oxygen saturation values were observed in patients after the procedure. Clinically significant methemoglobinemia (oxygen saturation < 90%) was detected in only one patient. We suggest that caution be exercised in patients with low baseline oxygen saturation or pulmonary comorbidities. Additionally, our study revealed that more significant decreases in oxygen saturation were observed in patients with methemoglobin levels above 10%. In the case of Pay et al.,[14] a 76-year-old patient developed methemoglobinemia

after using 800 mg prilocaine for pacemaker implantation and the patient's methemoglobin levels gradually decreased to the normal range, following methylene blue treatment. One of our patients who developed clinically symptomatic methemoglobinemia (dyspnea, oxygen saturation <90%) was followed up in the intensive care unit for 24 hours. The patient was given oxygen therapy and closely monitored. After 24 hours, our patient, whose clinical complaints improved and whose methemoglobin values dropped below 10%, was transferred from the intensive care unit to the cardiology clinic. Our patient was relieved with symptomatic treatment during the intensive care unit treatment period and methylene blue was not required in the treatment.

A significant relationship was found between the amount of prilocaine administered and higher methemoglobin levels. Elevated methemoglobin levels were also associated with higher creatinine levels, suggesting that caution should be exercised when using prilocaine in patients with renal failure. In a study by Kane et al.,[15] which examined 28,478 cases of local anesthetic administration during TEE, a significantly higher incidence of methemoglobinemia was observed in anemic patients. In our study, higher methemoglobin levels were found in patients with lower hemoglobin levels. Additionally, while Kane et al.[15] found no relationship between methemoglobinemia and BMI, our study identified a significant correlation between lower BMI and higher methemoglobin levels.

Limitations

The study was conducted at a single center and the number of cases included was limited. Additionally, the laboratory parameters available for analysis were few, which may have constrained the scope of the findings. The fact that patients do not have comorbidities limits the relationships between other diseases and the results. One of the limitations of the study is the lack of records of the subtypes of operations performed on the patients. The follow-up of the cases was done for a limited time and long-term follow-up is not available. The retrospective, single-center nature of the study affects the potential for case selection and limits its attribution to the entire population.

Conclusion

Methemoglobin levels significantly increased after ICD/CRT procedures with prilocaine. However, clinically significant cases are rare. Methemoglobin elevation is associated with factors such as BMI, creatinine and hemoglobin levels. Further multicenter studies are needed to elucidate these associations more clearly.

Ethics Committee Approval: Ethics committee approval was obtained from the Kütahya Health Sciences University Rectorate Non-Interventional Clinical Research Ethics Committee (Approval Number: 2021/40, Date: 05.03.2021).

Informed Consent: Written informed consent was obtained from all participants.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Association of the C-Reactive Protein to Albumin Ratio with the No-Reflow Phenomenon After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis

C-Reaktif Protein / Albümin Oranının Perkütan Koroner Girişim Sonrası No-Reflow Fenomeni ile İlişkisi: Sistematik Bir İnceleme ve Meta-Analiz

ABSTRACT

The no-reflow (NR) phenomenon, a complication of percutaneous coronary intervention (PCI), is associated with poor cardiovascular outcomes. Identifying reliable predictors of NR is crucial for risk stratification and improving clinical outcomes. The C-reactive protein (CRP) to albumin ratio (CAR), a marker of systemic inflammation, has been proposed as a potential predictor of NR. This systematic review and meta-analysis aimed to evaluate the relationship between CAR and NR following PCI. A comprehensive literature search was conducted in the Cochrane, Embase, and PubMed databases, following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. Studies assessing the predictive value of CAR for NR were included. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a random-effects model. Heterogeneity was assessed using Cochrane's Q and I^2 statistics. Four studies comprising a total of 2,068 patients were included. The pooled analysis showed a significant association between elevated CAR and an increased risk of NR (OR: 2.34; 95% CI: 1.19–4.60; P = 0.01; I^2 = 96%). Elevated CAR is associated with an increased risk of NR after PCI, indicating its potential as a prognostic biomarker. However, the high heterogeneity among studies highlights the need for large-scale research to confirm its clinical applicability.

Keywords: C-reactive protein to albumin ratio, meta-analysis, no-reflow phenomenon, percutaneous coronary intervention

ÖZET

Perkütan koroner girişim (PKG) sonrası no-reflow (NR) fenomeni olumsuz kardiyovasküler sonuçlarla ilişkilidir. NR'nin güvenilir öngörücülerini belirlemek, risk sınıflandırması ve klinik sonuçları iyileştirmek için çok önemlidir. Sistemik inflamasyonun bir belirteci olan CRP-albümin oranı (CAO), NR'nin potansiyel bir öngörücüsü olarak önerilmiştir. Bu sistematik inceleme ve meta-analiz, CAO ile PKG sonrası NR oluşumu arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır. PRISMA 2020 yönergelerini izleyerek PubMed, Cochrane ve Embase veri tabanlarında kapsamlı bir literatür araştırması yapıldı. NR için CAO'nun öngörücü değerini değerlendiren çalışmalar dahil edildi. %95 güven aralıkları (GA) ile birleştirilmiş olasılık oranları (OR'ler) rastgele etki modeli kullanılarak hesaplandı. Heterojenlik Cochrane'in Q ve I^2 istatistikleri kullanılarak değerlendirildi. 2.068 hastayı kapsayan dört çalışma dahil edildi. Birleştirilmiş analiz, daha yüksek CAO ile artmış NR riski arasında anlamlı bir ilişki olduğunu gösterdi (OR: 2,34; %95 GA: 1,19–4,60; P = 0,01; I^2 = %96). Yükselmiş CAO'nun PKG'den sonra NR ile ilişkili olduğunu bulduk, bu da prognostik bir biyobelirteç olarak potansiyel faydasını göstermektedir. Ancak, yüksek heterojenlik, klinik uygulanabilirliğini doğrulamak için büyük ölçekli çalışmalara olan ihtiyacı vurgulamaktadır.

Anahtar Kelimeler: CRP-albümin oranı, meta-analiz, no-reflow fenomeni, perkütan koroner girişim

REVIEW
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Percutaneous coronary intervention (PCI) is a critical procedure used to treat patients with coronary artery disease (CAD), particularly those experiencing acute coronary syndrome (ACS).[1] However, a significant challenge during PCI is the occurrence of the no-reflow (NR) phenomenon, a condition in which myocardial perfusion fails to recover despite successful coronary artery reperfusion.[2] The NR phenomenon is associated

with adverse outcomes, including life-threatening arrhythmias, heart failure, prolonged hospital stay, and increased mortality.[3] Identifying reliable predictors of NR could improve patient prognosis and support clinical decision-making.

Recent studies have demonstrated a link between inflammatory markers and the development of NR following PCI.[4-6] Among these markers, the C-reactive protein (CRP) to albumin ratio (CAR) has attracted interest for its ability to reflect systemic inflammation, a key contributor to the pathophysiology of NR.[4,6] Elevated CRP levels, a marker of inflammation, are commonly associated with atherosclerosis and its complications, while lower albumin levels are linked to increased vascular dysfunction and thrombosis.[7,8]

The aim of this systematic review and meta-analysis is to examine the association between the CRP-albumin ratio and the occurrence of NR following PCI. By pooling data from observational studies, we assess whether CAR may serve as an independent predictor of NR in PCI patients and explore its potential role in clinical practice.

Materials and Methods

This systematic review and meta-analysis were conducted and reported in accordance with the guidelines outlined in the Cochrane Collaboration Handbook for Systematic Reviews of Interventions, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) statement.[9,10] The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42025643272.

Search Strategy

A systematic search was conducted across the Cochrane Library, Embase, and PubMed databases. In addition, the reference list of included studies and relevant systematic reviews were screened to identify any additional eligible studies. The full search strategy for each database is provided in the Supplemental Material. The search was performed up to February 15, 2024.

Eligibility Criteria, Data Extraction, and Study Outcomes

Studies were included in the meta-analysis based on the following eligibility criteria:

1. Observational studies (prospective or retrospective);
2. Studies that compared patients who developed NR after PCI with those who did not;
3. Studies that performed multivariate regression analyses to assess whether CAR was an independent predictor of NR.

Exclusion criteria included studies with overlapping patient populations, conference abstracts, case reports, case series, and studies published in languages other than English.

Three investigators independently conducted the data search, study selection, and data extraction. Any disagreements were resolved by consensus after a thorough review of the full articles and eligibility criteria, in consultation with the senior author.

ABBREVIATIONS

ACS	Acute coronary syndrome
CAD	Coronary artery disease
CAR	C-reactive protein to albumin ratio
CRP	C-reactive protein
LDL	Low-density lipoprotein
MOOSE	the Meta-Analysis of Observational Studies in Epidemiology
NR	No-reflow
NSTEMI	Non-ST-elevation myocardial infarction
CI	Confidence intervals
OR	Odds ratio
PCI	Percutaneous coronary intervention
PRISMA	the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
ROBINS-I	The Risk of Bias in Non-Randomized Studies of Interventions
SCAD	Stable coronary artery disease
STEMI	ST-elevation myocardial infarction
SVG	Saphenous vein graft

Quality Assessment

The Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool was used to assess the risk of bias for each included study.[11] Two independent investigators performed the assessments, and any disagreements were resolved in consultation with the senior author. Sensitivity analyses were conducted using the "leave-one-out" method.

Statistical Analysis

All data analyses were performed in accordance with Cochrane recommendations.[12] Binary endpoints were analyzed using the Mantel-Haenszel method with a random-effects model. The odds ratio (OR) and 95% confidence interval (CI) were used as measures of effect size. All studies analyzed CAR as a continuous variable, and ORs were extracted to reflect changes in outcomes per 1-unit increase in CAR. Heterogeneity was assessed using Cochrane's Q statistic and the Higgins and Thompson I2 statistic. Heterogeneity was considered significant if the p-values were less than 0.10 and the I2 value exceeded 25%. Statistical analyses were performed using Review Manager version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Artificial Intelligence Disclosure

We confirm that no artificial intelligence (AI)-based tools, including chatbots, large language models (LLMs), or image generators, were used in the creation of this meta-analysis.

Results

Study Selection and Baseline Characteristics

As illustrated in Figure 1, the initial search yielded 613 records. After removing duplicates, 11 studies were selected for full-text review. Of these, four studies met the inclusion criteria.[4,6,13,14] A total of 2,068 patients were included across the four studies. Among them, 593 patients (28.7%) were in the NR group, and 1,475 patients (71.3%) were in the non-NR group. Table 1 summarizes

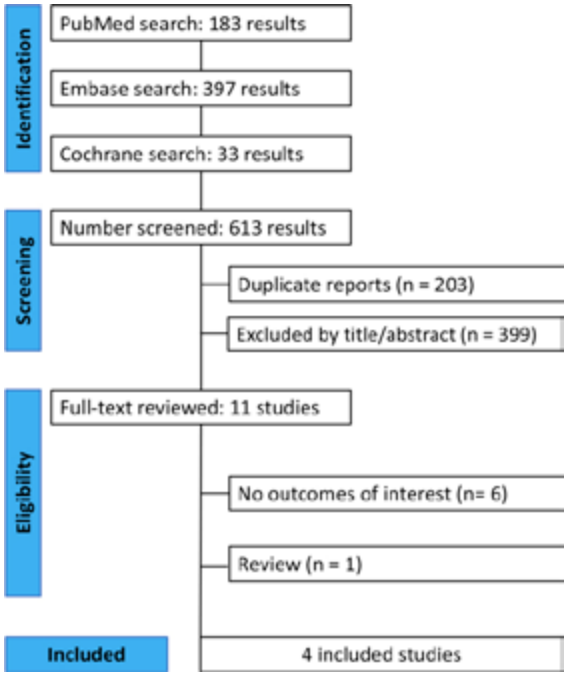

Figure 1. PRISMA flow diagram of study screening and selection.

the characteristics of the included studies. Two studies enrolled patients presenting with acute ST-elevation myocardial infarction (STEMI),[6,14] one study included patients with non-ST-elevation myocardial infarction (NSTEMI),[13] and one focused on patients undergoing PCI in a saphenous vein graft (SVG).[4]

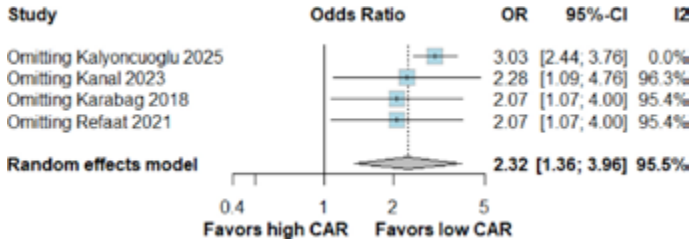

Figure 2. The heterogeneity decreased from I^2 = 95.5% to 0% upon omitting Kanyoncuoglu et al.(13) in the leave-one-out analysis.

Quality Assessment

The included studies were assessed as having a moderate overall risk of bias (Appendix 1). In the sensitivity analysis, heterogeneity decreased from I^2 = 95.5% to 0% after omitting the study by Kalyoncuoglu et al.,[13] in 2025 (Figure 2).

Endpoints

A pooled analysis of 593 patients in the NR group and 1,475 in the non-NR group demonstrated a significant association between elevated CAR and the risk of NR in patients undergoing PCI (OR: 2.34; 95% CI: 1.19–4.60; P = 0.01; I2 = 96%) (Figure 3).

Table 1. Baseline Characteristics of Included Studies

Study, Year	Population	No. of Patients, (NR/No NR)	Female, % (NR/No NR)	Age[a], years (NR/No NR)	DM, % (NR/No NR)	HTN, % (NR/No NR)	Current Smoker, % (NR/No NR)	LVEF[a] (NR/No NR)
Kalyoncuoglu et al.,[13] 2025	NSTEMI	30/179	23.3/20.1	56/56	30/27.9	43.3/55.3	50/46.9	47.0/50.1
Kanal et al.,[4] 2023	PCI of SVGb	48/194	21.3/24.4	65.7/65.0	67.3/40.4	73.5/64.6	36.4/30.3	42.0/50.0
Karabag et al.,[6] 2018	Acute STEMI	343/874	20.7/17.6	59/56	29.4/20.5	45.2/38.4	47.5/57.2	41.13/48.90
Refaat et al.,[14] 2021	Acute STEMI	172/228	25.6/31.6	65.21/56.61	69.8/43.9	69.8/43.9	60.5/61.4	42.26/46.37

[a]Mean or median; [b]Includes both acute coronary syndrome and stable coronary artery disease patients. DM, Diabetes Mellitus; HTN, Hypertension; LVEF, Left Ventricular Ejection Fraction; NR, No-Reflow; NSTEMI, Non-ST-Elevation Myocardial Infarction; PCI, Percutaneous Coronary Intervention; STEMI, ST-Elevation Myocardial Infarction; SVG, Saphenous Vein Graft.

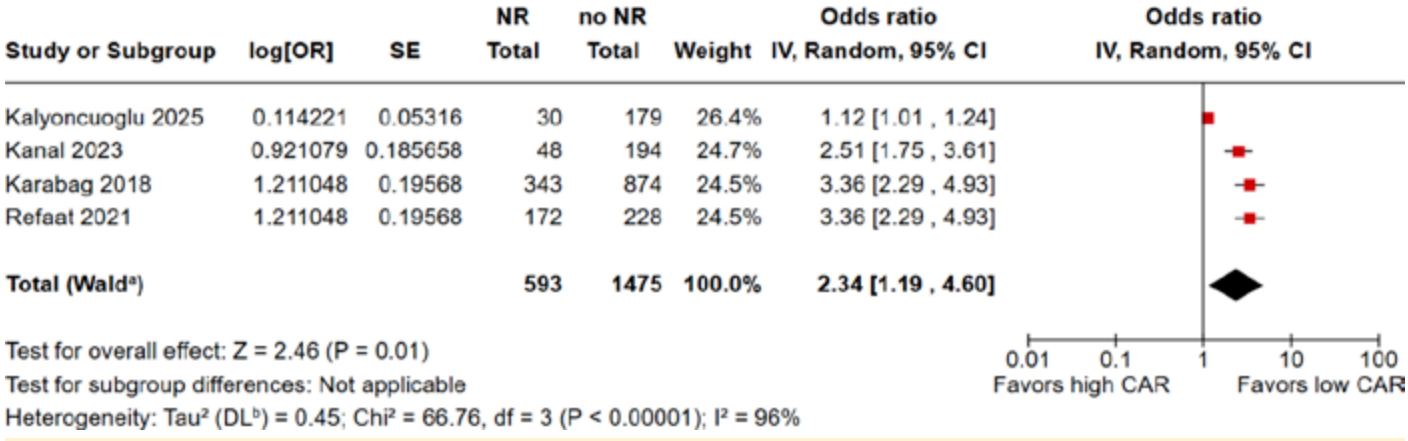

Figure 3. A CRP albumin ratio had a significantly higher rate association of no-reflow in patients undergoing percutaneous coronary intervention.

Discussion

This systematic review and meta-analysis, which included four studies comprising 2,068 patients, compared those who developed NR after PCI to those who did not. The primary finding from the pooled analysis was that a higher CAR was significantly associated with an increased risk of NR in patients undergoing PCI, whereas a lower CAR was associated with a reduced risk.

PCI is a complex procedure, and the NR phenomenon can further complicate clinical outcomes. NR has been linked to adverse events, including an increased risk of malignant arrhythmias, heart failure, and mortality.[1,2,15]

Previous studies suggest that NR occurs more frequently during PCI for ACS compared with elective procedures for stable coronary artery disease (SCAD).[3,16,17] The higher incidence in ACS has been attributed to several factors, including a greater thrombus burden, prolonged ischemia, and more complex lesion morphology—such as ruptured or lipid-rich plaques—which are more common in ACS than in SCAD.[16–19] Given these contributing factors, we aimed to evaluate the overall inflammatory burden in NR versus non-NR populations using the CAR, as ACS typically triggers a significant inflammatory response due to these underlying pathological processes.

Inflammation is a key factor in the progression of atherosclerosis.[20] C-reactive protein, as a biomarker of inflammation, is significantly associated with the advancement of atherosclerotic disease.[7] Research indicates that CRP elevates the production of reactive oxygen species, facilitates the uptake of oxidized low-density lipoprotein (LDL), promotes endothelial dysfunction, and triggers cell apoptosis. Furthermore, it stimulates vascular smooth muscle cell proliferation and increases the likelihood of plaque rupture.[7,21] In contrast, albumin functions as a negative acute-phase protein and serves as an indicator of inflammation severity in critically ill individuals.[22] Decreased serum albumin levels are significantly associated with endothelial dysfunction, increased blood viscosity, and heightened platelet aggregation.[8] Additionally, lower albumin concentrations have been linked to poorer in-hospital outcomes, greater stent restenosis, and more severe CAD.[23,24]

Our meta-analysis revealed that patients who developed NR had significantly higher CAR values compared to those who did not. One potential explanation is that the heightened inflammatory response in these patients results in elevated CRP levels alongside reduced albumin levels. A greater plaque burden may further intensify this inflammatory reaction, contributing to increased lesion complexity, larger occlusions, and more extensive myocardial damage—factors that could further elevate CAR.[25–27] However, no standardized cutoff values currently exist to correlate CAR with the severity of overall disease burden, nor were there consistency in the timing of sample collection in relation to the onset of the event. As a result, definitive risk stratification could not be established.

Limitations

Our study has several limitations. First, all included studies were observational, as no randomized controlled trials (RCTs) on this subject are currently available. Observational studies are inherently more susceptible to various forms of bias, particularly confounding bias, which occurs when the relationship between exposure and outcome is influenced by one or more unmeasured variables. Second, significant heterogeneity was observed across studies. Notably, sensitivity analysis using the leave-one-out method revealed that heterogeneity dropped to zero after excluding the study by Kalyoncuoglu et al.,[13] suggesting that this study was the primary source of variability. Third, there was no standardized protocol for the timing of blood sample collection, which may have influenced the results, particularly given the relatively short half-lives of CRP and albumin. Fourth, we were unable to analyze the association between CAR and clinical outcomes such as cardiac death at follow-up, as these endpoints were not reported in the included studies, except for Kanal et al.[4] Finally, the majority of the included studies were conducted in a single country, which raises concerns regarding the external validity of our findings.

Conclusion

We found that higher CAR levels were associated with an increased risk of NR following PCI, suggesting its potential utility as a prognostic biomarker. These findings indicate that CAR, as a marker of systemic inflammation, may serve as a valuable tool for predicting NR and could support improved risk stratification and clinical decision-making.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Peer-review: Externally peer-reviewed.

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Appendix 1. Risk of bias summary for non-randomized studies (ROBINS-I)

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgement
Kalyoncuoğlu et al.[13] 2025	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Karabağ et al.[6] 2018	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Kanal et al.[4] 2023	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Refaat et al.[14] 2021	Moderate	Low	Low	Moderate	Low	Moderate	Moderate	Moderate

Full search strategy for each database

PubMed

("No-Reflow Phenomenon"[Mesh] OR "no reflow phenomenon" OR "no-reflow" OR "microvascular obstruction") AND ("C-reactive Protein/Albumin " OR "C-reactive protein" OR "C-Reactive Protein"[Mesh] OR "CRP" OR "C-reactive protein to albumin" OR "CAR" OR "CRP Albumin Ratio" OR "Albumins"[Mesh] OR "Albumin")

Embase

('no reflow phenomenon'/exp OR 'no reflow phenomenon' OR 'no-reflow' OR 'microvascular obstruction') AND ('c-reactive protein/albumin' OR 'c-reactive protein' OR 'C reactive protein'/exp OR 'crp' OR 'c-reactive protein to albumin' OR 'car' OR 'crp albumin ratio' OR 'albuminoid'/exp OR 'albumin')

Cochrane Library

("no reflow phenomenon" OR "no-reflow" OR "microvascular obstruction") AND ("C-reactive Protein/Albumin " OR "C-reactive protein" OR "CRP" OR "C-reactive protein to albumin" OR "CAR" OR "CRP Albumin Ratio" OR "Albumin")

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New Drugs for Resistant Hypertension: Pending Issue?

İlaç Dirençli Hipertansiyon İçin Yeni İlaçlar: Hâlâ Çözülememiş Bir Sorun mu?

ABSTRACT

Antihypertensive pharmacological treatment, based on currently available drugs, has been shown to reduce the cardiovascular risk profile of treated hypertensive patients by lowering elevated blood pressure. However, the cardiovascular risk in treated hypertensive patients remains elevated. This highlights the need to develop new antihypertensive drugs capable of normalizing the risk associated with high blood pressure. This paper aims to review new antihypertensive drugs for the treatment of drug-resistant hypertension. In particular, it focuses on the results obtained with non-steroidal mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, brain renin-angiotensin blockers, hepatic angiotensinogen inhibitors, atrial natriuretic peptides, and endothelin-1 receptors antagonists.

Keywords: Antihypertensive treatment, new antihypertensive drugs, resistant hypertension

ÖZET

Mevcut ilaçlara dayanan antihipertansif farmakolojik tedavinin, yüksek kan basıncını düşürerek tedavi edilen hipertansif hastaların kardiyovasküler risk profilini azalttığı gösterilmiştir. Ancak, tedavi edilen hipertansif hastalarda risk yüksek kalmaya devam etmektedir. Bu durum, kontrol altına alınamayan yüksek kan basıncına bağlı kardiyovasküler riski normalleştirebilecek yeni antihipertansif ilaçların geliştirilmesi için bir gerekçe oluşturmaktadır. Bu makale, ilaçlara dirençli hipertansiyon tedavisinde kullanılabilecek yeni antihipertansif ilaçların gözden geçirilmesini amaçlamaktadır. İnceleme özellikle steroidal olmayan mineralokortikoid reseptör antagonistleri, aldosteron sentaz inhibitörleri, beyin renin-anjiotensin blokerleri, hepatik anjiyotensinojen inhibitörleri, atriyal natriüretik peptitler ve endotelinin 1 reseptör antagonistleri ile elde edilen sonuçlara odaklanacaktır.

Anahtar Kelimeler: Antihipertansif tedavi, yeni antihipertansif ilaçlar, dirençli hipertansiyon

REVIEW
DERLEME

Hypertension (HT) is one of the most common risk factors contributing to the high incidence of cardiovascular and renal disease worldwide.[1] A wide range of available antihypertensive drugs, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), thiazide diuretics, beta-blockers, and their combinations, can effectively reduce blood pressure (BP), with a significant associated decrease in the risk of hypertension-mediated organ damage.[2] However, BP control is achieved in only about 40% of patients in Europe1. Several reasons have been proposed to explain this lack of BP control in treated hypertensive patients. These include the routine use of monotherapy, low rates of HT awareness, physician inertia in up-titrating antihypertensive drugs or initiating combination therapy, and, finally, poor patient adherence to prescribed treatment regimens.[3] Additionally, in a variable percentage of patients (12%–18%), HT remains difficult to control despite the use of three to four drugs from different classes, administered at recommended daily dosages.[4,5] The prevalence of resistant hypertension (RHT) is particularly high in patients with hyperaldosteronism, advanced chronic kidney disease (CKD), diabetes, the elderly, as well as those with obesity and obstructive sleep apnea.[4] Similar to essential HT, RHT is associated with a high risk of HT-mediated organ damage and cardiovascular events.[5] Hyperaldosteronism, characterized by salt retention and volume expansion, along with sympathetic nervous system hyperactivation, increased secretion of endothelin-1, and altered levels of natriuretic peptides, represents the most common set of pathophysiological mechanisms involved in the development and progression of RHT.[6]

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Current Therapeutic Strategy

The aldosterone-mineralocorticoid receptor axis plays an important role in BP regulation. Elevated circulating aldosterone plasma levels, by promoting renal sodium retention and potassium excretion, are involved in the pathophysiology of both HT and RHT.[7] Currently, spironolactone and eplerenone have an established role in the treatment of heart failure and are also used as fourth-line agents for RHT in patients with plasma potassium levels < 4.5 mmol/L and an estimated glomerular filtration rate (eGFR) > 45 mL/min/1.73 m^2. Notably, the PATHWAY-2 trial (Prevention And Treatment of Hypertension With Algorithm based Therapy-2), a double-blind, randomized, placebo-controlled study, demonstrated that spironolactone (25–50 mg/day), when added to existing antihypertensive therapy, was more effective in reducing BP (Table 1) and achieving BP control in patients with RHT compared with placebo, bisoprolol, and doxazosin.[8] A recent large meta-analysis[9] also confirmed the efficacy of spironolactone in lowering both office and 24-hour ambulatory BP. However, the same analysis reported that, compared with other antihypertensive drugs, spironolactone did not significantly reduce office diastolic BP (Table 1). Despite its effectiveness, the therapeutic use of spironolactone in clinical practice is limited by the risk of hyperkalemia, particularly in patients with advanced CKD or those treated with ACE inhibitors or ARBs, as well as its anti-androgenic and progesterone receptor agonist effects, which can lead to gynecomastia and sexual dysfunction. The combination of spironolactone with potassium binders such as patiromer reduces the risk of hyperkalemia,[10] but does not prevent the hormonal side effects.

Eplerenone is a second-generation mineralocorticoid receptor antagonist, with a lower affinity compared to spironolactone.[11] Several studies, summarized in a meta-analysis,[12] have documented the effectiveness of eplerenone (50–200 mg/day) in the treatment of essential HT. However, strong evidence regarding its efficacy in patients with RHT is lacking. Although few direct comparative studies between eplerenone and spironolactone are available, eplerenone has the notable advantage of causing fewer hormonal side effects than spironolactone. Nonetheless, it also presents some drawbacks, such as higher cost, potential drug-drug interactions due to metabolism via cytochrome P450 pathway, and a shorter half-life, which necessitates twice-daily administration.[11] Like spironolactone, eplerenone is associated with the risk of hyperkalemia, especially in patients with chronic kidney disease or those receiving ACE inhibitors or ARBs.[11] To achieve better BP control in patients with RHT, new pharmacological agents targeting various key pathophysiological pathways have been developed and are currently either in clinical development or have recently been approved.

The aim of this narrative review is to provide an update on emerging drugs for the treatment of RHT. The results obtained with these drugs in patients with essential HT will also be discussed.

Materials and Methods

We searched PubMed, Google Scholar, and Medline for original randomized clinical trials and open-label studies published between 2019 and 2024, involving new drugs tested in patients with RHT. The following search terms were used: "resistant HT," "treatment of RHT," "drugs for RHT," "new drugs for RHT," and "uncontrolled HT." Studies involving patients with secondary HT, duplicate publications, and expert opinions were excluded. We did not follow a standard protocol for systematic reviews, as this paper is a narrative review aimed at providing an overview of the available evidence. Data on BP reduction is reported as absolute values, while placebo-corrected results are presented in Table 1. Eligible publications were independently selected by two reviewers (FF, RR).

ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitors
ANP	Atrial natriuretic peptides
APA	Aminopeptidase A
ARBs	Angiotensin receptor blockers
AT 1	Angiotensin 1
AT 2	Angiotensin type 2
BLOCK-CKD	Blood pressure lowering with ocedurenone in chronic kidney disease and resistant hypertension
BP	Blood pressure
BrigHTN	Blood pressure reduction in resistant hypertension with baxdrostat
CCBs	Calcium channel blockers
CKD	Chronic kidney disease
DBP	Diastolic blood pressure
EARLY-NH	Efficacy of Esaxerenone in early treatment of nocturnal hypertension
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ET-1	Endothelin-1
EXCITE-HT	Esaxerenone Comparative evaluation for optimal treatment in uncontrolled hypertension
FDA	Food and Drug Administration
FRESH	Firibastat in Resistant Hypertension
HT	Hypertension
MANP	M-atrial natriuretic peptide
PATHWAY-2 trial	prevention and treatment of hypertension with algorithm-based therapy-2
RECISION	Placebo-Controlled Randomized Study of the Selective Endothelin A Receptor Antagonist Aprocitentan in Resistant Hypertension
RHT	Resistant hypertension
SBP	Systolic blood pressure
Target-HTN	Treatment with lorundrostat in adults with uncontrolled hypertension and elevated aldosterone levels

Emerging Drug Classes for RHT (Figure 1)

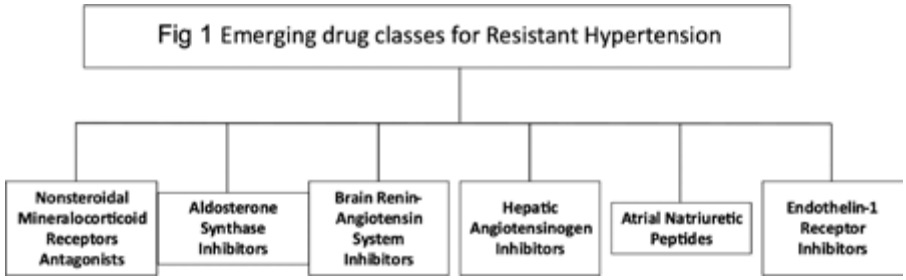
Nonsteroidal Mineralocorticoid Receptor Antagonists

To avoid the hormonal side effects of spironolactone and eplerenone, as well as the risk of hyperkalemia, several nonsteroidal mineralocorticoid receptor antagonists have been approved or are currently under clinical investigation. Esaxerenone, a highly selective nonsteroidal mineral receptor antagonist,[13] has been tested in patients with uncontrolled HT. The multicenter, randomized, open-label, parallel-group, EXCITE-HT (Esaxerenone Comparative Evaluation for Optimal

Table 1. Blood pressure reduction (placebo or active comparator corrected) in patients with resistant or essential hypertension

Drug class	Office SBP/DBP (mmHg)	24-h Ambulatory SBP/DBP (mmHg)
Mineralocorticoid receptor antagonists		
Spironolactone[8]	20.1/-5.7**	-10.3/-3.9**
Office SBP[9]	-6.0**/-0.5	-6.9*/-3.0**
Eplerenone[12,&&]	-9.2/-4.1**	
Nonsteroidal mineralocorticoid receptor antagonists		
Esaxerenone[14]		
Morning home BP	-2.2*/-0.6	
Bedtime home BP	-2.2/-0.9	
Office BP	-3.4/-1.5	
Esaxerenone[17,&&]		
2.5 mg	-0.23/-0.4	
5.0 mg	-4.4/-2.1**	
Ocedurenone[20,21]		
0.25 mg	-7.0*	
0.50 mg	-10.2**	
CKD patients		
0.25 mg	-9.3	
0.50 mg	-10.0	
Diabetes patients		
0.25 mg	-6.9	
0.50 mg	-11.6	
Albuminuria patients		
0.25 mg	-13.1	
0.50 mg	-12.3	
Aldosterone synthase inhibitors		
Baxdrostat[25]		
0.5 mg	-2.7/0.6	
1.0 mg	-8.1**/-2.6	
2.0 mg	-11.0/-5.1**	
Lorundrostat[28]		
12.5 mg	-1.5/-2.1	-5.2
50 mg	-9.6**/-5.5*	-1.8
100 mg	-7.8*/-4.1	-8.9
Brain Renin-angiotensin system inhibitors		
Firibastat[30]	-4.7	-2.7
Hepatic angiotensinogen inhibitors		
IONIS-AGT-LRx[33,&&]	-6.0/-3.0	
Hepatic angiotensinogen inhibitors		
Zilebesiran[35,&&]		
150 mg	-9.6**	-14.1**
300 mg	-12.0**	-16.7**
600 mg	-9.1**	-15.7**
Endothelin-1 receptor inhibitors		
Aprocitentan[44]		
12.5 mg	-3.8/-3.9**	-4.2/-4.3
25 mg	-3.7/-4.5**	
Aprocitentan[45,&&]		
5 mg	-2.4/-1.3	0.9/-0.9
10 mg	-7.0/-4.9**	-4.0/-4.0**
25 mg	-9.9/-7.0**	-4.8/-5.9**
50 mg	-7.6/-4.9**	-3.6/-4.4**

Data are shown as systolic and diastolic blood pressure reductions compared to baseline values. Asterisks (*P < 0.05, **P < 0.01) indicate statistical significance versus control. &&, Essential hypertension; ABPM, Ambulatory blood pressure monitoring; CKD, Chronic kidney disease; DBP, Diastolic Blood pressure; SBP, Systolic blood pressure.



Treatment in Uncontrolled Hypertension) trial[14] compared esaxerenone (2.5–5.0 mg/day) with trichlormethiazide, both administered as add-on therapy to either an ARB or a CCB, in patients with uncontrolled HT. After 12 weeks, BP reductions in home morning, bedtime, and office measurements were not significantly different between the esaxerenone and trichlormethiazide groups. The percentage of subjects achieving morning home BP control (BP < 140/90 mmHg) was nearly identical between the two groups (60.8% vs. 55.8%). Moreover, there was no significant difference between the two drugs in reducing the urinary albumin-to-creatinine ratio (UACR: -38.9% vs. -41.9%) in the subgroup of patients (26%) with diabetes and baseline albuminuria. Overall, the effect of esaxerenone in patients with uncontrolled BP was comparable to that of the diuretic trichlormethiazide (Table 1).

Another open-label study, the EARLY-NH (Efficacy of Esaxerenone in Early Treatment of Nocturnal Hypertension) trial,[15] evaluated the efficacy of esaxerenone in patients with uncontrolled nocturnal HT (systolic BP ≥ 120 mmHg). After 12 weeks of treatment, esaxerenone (2.5–5.0 mg/day), added to either an ARB or a CCB, significantly reduced home nocturnal systolic/diastolic BP, as well as morning and bedtime BP. A post hoc analysis of this study[16] showed that a higher percentage of patients treated with esaxerenone (63.6%) achieved the target nighttime systolic BP of < 120 mmHg. This finding is clinically relevant, as nocturnal HT is associated with an increased risk of cardiovascular events. However, both studies have some limitations: a) the trials were open-label, b) the treatment duration was relatively short, and c) the definition of RHT used in the studies does not align with the current standard definition.

The antihypertensive properties of esaxerenone have also been demonstrated in patients with essential HT, showing a similar BP-lowering effect when used either as monotherapy or in combination with ARBs or CCBs. A recent meta-analysis[17] reported no significant difference between esaxerenone 2.5 mg/day and eplerenone 50 mg/day in reducing systolic BP; however, the highest dose of esaxerenone (5 mg/day) was found to be more effective (Table 1). In patients with type 2 diabetes[18] and proteinuria (urinary albumin-to-creatinine ratio 45 to < 300 mg/g, who were already receiving treatment targeting the renin-angiotensin system, esaxerenone (1.25–2.5 mg/day) was more effective than placebo (44% vs. 11%, respectively) in achieving proteinuria remission (UACR < 30 mg/g creatinine). In these patients, systolic/diastolic BP was significantly reduced from baseline by 10/5 mmHg. Treatment with esaxerenone was associated with elevated renin activity and plasma aldosterone levels, indicating effective mineral receptor inhibition. No hormone-related adverse effects were reported, and there was no significant difference compared to placebo in terms of drug-related side effects or treatment discontinuation.[17,19] Hyperkalemia (≥ 6.0 or ≥ 5.5 mEq/L) occurred in 9.0% of patients treated with esaxerenone compared to 2.0% in the placebo group. Increases in plasma potassium were particularly evident in individuals with baseline potassium levels ≥ 4.5 mEq/L or with eGFR < 60 mL/min.[18] Therefore, plasma potassium and eGFR should be regularly monitored during esaxerenone treatment. This recommendation is supported by findings from the ESAX-DN (Esaxerenone in Patients With Type 2 Diabetes and Microalbuminuria) trial,[18] conducted in patients with type 2 diabetes and microalbuminuria, which showed a greater reduction in estimated glomerular filtration rate with esaxerenone compared to placebo (-11% vs. -1%). Considering all these results, esaxerenone, when added to ARBs or CCBs, can be considered an effective option for patients with essential HT, including those with type 2 diabetes and chronic kidney disease. Esaxerenone has been approved in Japan for this indication. However, studies evaluating its antihypertensive effectiveness in RHT, particularly in Caucasian populations, are still lacking.

Two other new pharmacological compounds in the nonsteroidal mineral receptor antagonist class are ocedurenone and finerenone. Ocedurenone, a highly selective receptor antagonist, is under development for RHT, particularly in patients with CKD. The BLOCK-CKD (Blood Pressure Lowering With Ocedurenone in Chronic Kidney Disease and Resistant Hypertension) trial,[20] a Phase 2b, multicenter, randomized, double-blind, placebo-controlled study, was conducted in patients with RHT and stage 3b/4 CKD. After 84 days of treatment, systolic BP was significantly reduced with both 0.25 mg and 0.50 mg daily doses of ocedurenone compared to placebo, while diastolic BP did not differ between the groups. In 77.2% of patients with baseline proteinuria, the urinary albumin-to-creatinine ratio remained unchanged. A subsequent subgroup analysis[21] demonstrated that both doses of ocedurenone reduced systolic BP (placebo-corrected) even in patients with type 2 diabetes, stage 4 CKD, and high albuminuria (Table 1). Hyperkalemia (≥ 5.6 to ≤ 6.0 mmol/L) was observed in 9.8% and 13.0% of patients receiving 0.25 mg and 0.5 mg of ocedurenone, respectively. This study, however, had some limitations: a) a small number of patients, b) the lack of a significant difference in diastolic BP between ocedurenone and placebo, c) the absence of 24-hour BP monitoring to confirm the diagnosis of RHT, and d) the short treatment duration (< 3 months). Therefore, the evidence supporting the effectiveness of ocedurenone remains limited. Long-term clinical trials with a larger sample size are needed to confirm its antihypertensive efficacy in routine clinical practice.

The other nonsteroidal selective mineralocorticoid receptor antagonist is finerenone. The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved finerenone for cardiovascular and renal protection in patients with diabetes and CKD. However, in patients with RHT and CKD, finerenone has been associated with a highly variable and lower reduction in office systolic BP compared to spironolactone.[22] Therefore, finerenone cannot be considered an effective antihypertensive drug.

Aldosterone Synthase Inhibitors

Another pharmacological approach to lowering elevated BP, particularly in RHT, is the inhibition of aldosterone synthesis through selective aldosterone synthase inhibitors. Selectivity is a crucial property of these compounds in order to avoid a reduction in plasma cortisol, as aldosterone synthase shares a similar chemical structure with 11β-hydroxylase, involved in cortisol synthesis.[23] Aldosterone plays a key role in the regulation of water and electrolyte homeostasis. Elevated plasma aldosterone levels induce vasoconstriction (through nitric oxide degradation and endothelin-1 release from endothelial cells), increase water and sodium reabsorption in the distal renal tubules, and consequently contribute to elevated BP and RHT.[23] Following the negative results with osilodrostat,[24] another aldosterone synthase inhibitor, baxdrostat, with significantly higher selectivity, has been tested in patients with RHT. The BrigHTN (Blood Pressure Reduction in Resistant Hypertension With Baxdrostat) trial, a Phase 2, multicenter, double-blind, placebo-controlled study,[25] randomized patients with RHT to receive baxdrostat (0.5, 1, or 2 mg/day) added to ACE inhibitors or ARBs and CCBs, or placebo, for 12 weeks. Baxdrostat significantly reduced systolic and diastolic BP at all three doses, with a statistically significant reduction observed at 1 mg and 2 mg. Diastolic BP was reduced only at the highest dose. Therefore, the 2 mg dose appears to be the most effective (Table 1). At this dose, a dose-dependent reduction in plasma and urinary aldosterone levels, along with a compensatory increase in renin activity, was observed, indicating effective aldosterone synthase inhibition. Plasma cortisol concentrations were not affected by any dose of baxdrostat, confirming its minimal effect on 11β-hydroxylase. Overall, the drug was well tolerated, and cases of hyperkalemia (5.5–6.3 mmol/L) were managed with temporary discontinuation of treatment. However, in the HALO (Hypertension and Aldosterone Synthase Inhibition with Lorundrostat) trial, another multicenter, randomized, Phase 2 study,[26,27] there was no statistically significant difference between baxdrostat and placebo in reducing systolic BP or in the proportion of patients achieving systolic BP control. The BrigHTN study also had two notable limitations: a) 24-hour BP monitoring was not performed to confirm the diagnosis of RHT, and b) the proportion of patients achieving BP control was not reported. Given the conflicting results between the BrigHTN and HALO trials, the efficacy and tolerability of baxdrostat require further confirmation.

Lorundrostat, another agent targeting aldosterone synthase, has also been evaluated in patients with RHT. The Target-HTN (Treatment With Lorundrostat in Adults With Uncontrolled Hypertension and Elevated Aldosterone Levels) study, a multicenter, placebo-controlled trial,[28] randomized patients with uncontrolled HT and low or normal plasma renin activity. In the subgroup with plasma renin ≤ 1.0 ng/mL/h and plasma aldosterone ≥ 1 ng/dL, lorundrostat (50 mg and 100 mg once daily for eight weeks) reduced office systolic BP more effectively than placebo. Interestingly, diastolic BP was reduced more with the 50 mg dose than with the 100 mg dose. The change in 24-hour BP monitoring was not statistically significant compared with placebo (Table 1). Office systolic BP reduction was similar in patients with both low and normal plasma renin levels. The percentage of subjects achieving BP control (< 130/80 mmHg) was higher with all doses of lorundrostat (42.9% vs. 30.0%) compared to placebo (23.3%). Aldosterone levels were reduced with all lorundrostat doses. No changes in plasma cortisol were reported, and only 3.6% of patients experienced hyperkalemia (> 6.0 mmol/L). This study had two major limitations: a) a small sample size, and b) the absence of BP monitoring to confirm the diagnosis of RHT. Therefore, further clinical trials are needed to better define the role of lorundrostat in the treatment of uncontrolled HT.

Brain Renin-Angiotensin System Inhibitors

Overactivation of the brain renin-angiotensin system plays a significant role in elevating BP. The enzyme aminopeptidase A (APA) is involved in the conversion of angiotensin II into angiotensin III, which has a high affinity for brain angiotensin 1 (AT 1) and type 2 (AT 2) receptors. This interaction leads to increased vasopressin release, heightened sympathetic neural outflow, and inhibition of the brain baroreflex activity.[29] Pharmacological blockade of APA activity reduces the effects of brain angiotensin III and, consequently, lowers BP. Several aminopeptidase A inhibitors have been synthesized, but only firibastat has been tested in clinical trials.[29] A Phase 2, placebo-controlled, crossover study[30] conducted in patients with uncontrolled HT showed that firibastat (250–500 mg twice daily) had effects on office and 24-hour mean BP; however, the difference compared to placebo was not statistically significant (Table 1). BP reduction was also observed in patients with essential HT, particularly in overweight or obese individuals,[31] where systolic/diastolic BP was significantly reduced by 9.5/4.2 mmHg compared to baseline values. Additionally, firibastat monotherapy lowered mean 24-hour systolic/diastolic BP, although it did not significantly affect nighttime BP. The subsequent FRESH (Firibastat in Resistant Hypertension) trial,[32,27] a randomized, double-blind, placebo-controlled study presented at the 2022 annual meeting of the American Heart Association, confirmed the lack of difference between firibastat and placebo in patients with RHT. These findings led to the discontinuation of firibastat's development.

Hepatic Angiotensinogen Inhibitors

Angiotensinogen, synthesized primarily in the liver, plays a central role in the pathophysiology of HT, serving as the precursor of both angiotensin I and II. Two drugs, IONIS-AGT-LRx and zilebesiran, are currently under evaluation in patients with RHT. The effects of IONIS-AGT-LRx, an antisense oligonucleotide,[33] have been assessed in two small, randomized, double-blind, placebo-controlled clinical trials. In patients with uncontrolled BP, the effect of IONIS-AGT-LRx (80 mg weekly via subcutaneous injection for eight weeks), added to ongoing antihypertensive therapy, was not statistically different from placebo in terms of overall BP reduction. However, a high percentage of subjects treated with IONIS-AGT-LRx achieved a systolic/diastolic BP

reduction of ≥ 10.0/5.0 mmHg. Similar findings were observed in subjects with controlled essential HT treated with IONIS-AGT-LRx as monotherapy (Table 1). Plasma angiotensinogen levels significantly decreased in both trials compared with placebo. The lack of BP reduction is likely due to the small sample sizes in these studies. Therefore, additional studies with different clinical protocols are currently underway.[33]

Zilebesiran is a ribonucleic acid (RNA) interference drug that targets hepatic angiotensinogen synthesis. Following the positive results of a Phase 1 trial,[34] which demonstrated a reduction in 24-hour ambulatory BP and plasma angiotensinogen levels, a Phase 2 multicenter, randomized, double-blind study (Kardia-1 [A Study of Zilebesiran in Adults With Mild to Moderate Hypertension]) was conducted in patients with mild to moderate HT.[35] After a washout period, patients were randomized to receive zilebesiran subcutaneously at 150 mg every six months, 300 mg every three to six months, or 600 mg every six months, or to placebo administered every three months. At three months post-administration, zilebesiran at all doses (150 mg, 300 mg every three to six months, and 600 mg every six months) significantly lowered both 24-hour ambulatory and office systolic BP. Similar results were maintained after six months of treatment. However, 26.8% of subjects assigned to zilebesiran required the addition of CCBs and/or diuretics, compared with 52.0% of subjects in the placebo group. Zilebesiran reduced plasma angiotensinogen levels by more than 90%, with an effect lasting up to six months. The ongoing Kardia-2 trial, along with other large-scale studies, will further evaluate the therapeutic role of zilebesiran, particularly in patients with RHT. Zilebesiran is a particularly promising drug, not only because it reduces both office and 24-hour ambulatory BP (Table 1), but also because its long-lasting antihypertensive effects may help improve patient adherence to treatment.

Atrial Natriuretic Peptides

Atrial natriuretic peptides (ANP) are secreted by atrial cardiomyocytes in response to plasma volume overload and play a key role in BP and renal homeostasis. Their mechanisms include inhibition of the renin-angiotensin-aldosterone system, reduction of renal sodium reabsorption, and induction of vasodilation. M-atrial natriuretic peptide (MANP) is an analog of ANP with high resistance to enzymatic degradation.[36] A small open-label study conducted in untreated hypertensive patients demonstrated the long-acting antihypertensive efficacy of MANP.[36] Subcutaneous doses of 1.0, 2.5, and 5 μg/kg once daily reduced systolic BP, although no clear dose-response relationship was observed. Diastolic BP responses showed wide variability. MANP increased renal sodium excretion, particularly during the first four hours after administration, and decreased plasma aldosterone levels. Treatment was associated with an increased heart rate, especially at doses of 2.5–5.0 μg/kg. An important limitation of this study was the small number of enrolled patients (n = 12). Another small, double-blind, placebo-controlled trial tested MANP in hypertensive patients with metabolic syndrome37, but found no significant difference between MANP and placebo. Therefore, doubts remain regarding the role of MANP as an antihypertensive agent, and future larger clinical trials are needed to confirm its BP-lowering effects.

Endothelin-1 Receptor Inhibitors

Endothelin-1 (ET-1) is synthesized by vascular endothelial cells and plays a physiological role in BP regulation through ET^A and ET^B receptors, which are primarily expressed on vascular smooth muscle and endothelial cells.[38-40] Some selective ET^A inhibitors, such as bosentan, ambrisentan, and macitentan, are approved for use in patients with pulmonary HT. Other agents (atrasentan, zibotentan, and sparsentan) are currently under clinical development for patients with type 2 diabetes and/or CKD.[39,43] Sitaxentan and avosentan were discontinued during development due to serious drug-related adverse events, particularly edema and heart failure.[39] Other endothelin-1 antagonists have high affinity for both ET^A and ET^B receptors. Among these, aprocitentan has been tested in patients with RHT[44] and essential HT.[45] The PRECISION (Placebo-Controlled Randomized Study of the Selective Endothelin A Receptor Antagonist Aprocitentan in Resistant Hypertension) trial, a Phase 3, multicenter, randomized, international study,[44] was conducted in patients with RHT. After a placebo run-in phase, patients were randomized through three subsequent clinical stages: a) a four-week double-blind period during which patients received aprocitentan (12.5 mg or 25 mg daily) or placebo, b) a 32-week single-blind phase during which all patients were treated with aprocitentan 25 mg daily, and c) a 12-week, double-blind, placebo-controlled, withdrawal phase in which patients were re-randomized to continue aprocitentan 25 mg daily or switch to placebo. This was followed by a 30-day safety observation period. Throughout the study, aprocitentan was used as an add-on to background antihypertensive therapy (valsartan, amlodipine, and hydrochlorothiazide). Unattended office systolic BP decreased from baseline by 15.3 mmHg and 15.2 mmHg with aprocitentan at doses of 12.5 mg/day and 25 mg/day, respectively. Office diastolic BP also decreased compared to placebo (Table 1). During phase [b], office systolic blood pressure (SBP) with aprocitentan continued to decline until the 20th week and then remained stable. In phase [c], office SBP was reduced by an additional 1.5 mmHg in the group that continued aprocitentan. The BP-lowering efficacy of aprocitentan has also been confirmed by 24-hour ambulatory BP monitoring (Table 1). Thus, when used as an add-on to other antihypertensive agents, aprocitentan demonstrates effective antihypertensive activity in patients with RHT. A Phase 2, double-blind, multicenter, dose-finding study[45] compared different doses of aprocitentan monotherapy with placebo and lisinopril (20 mg/day) in patients with essential HT. After an eight-week treatment period, a greater reduction in office BP from baseline was achieved with aprocitentan compared to both placebo and lisinopril. Additionally, aprocitentan reduced 24-hour ambulatory BP. The percentage of patients achieving diastolic blood pressure (DBP) < 90 mmHg at the end of treatment was 52.1%, 64.2%, and 57.4% with aprocitentan at doses of 10 mg, 25 mg, and 50 mg respectively, compared to 33.3% with placebo and 55.1% with lisinopril.

Aprocitentan was generally well tolerated. In the PRECISION study, mild to moderate fluid retention occurred in approximately 9% of subjects receiving 12.5 mg and 18% receiving 25 mg, particularly among patients with CKD. This side effect was reversible with the use of loop diuretics. Therefore, it is recommended to monitor hemoglobin levels and observe for signs of fluid retention or

heart failure. No hepatotoxicity or hyperkalemia was reported. All these findings suggest that aprocitentan at 12.5–25.0 mg/day, when added to conventional antihypertensive agents, can be considered a valid strategy for lowering BP in patients with RHT. In fact, aprocitentan has recently been approved by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of RHT.[46] Patients with chronic heart failure should be maintained in a euvolemic state, as some patients treated with aprocitentan in the PRECISION study[44] were hospitalized for heart failure.

Conclusion

This review summarizes the main characteristics of emerging drugs for the treatment of RHT, some of which have also been studied in essential HT. Therapeutic strategies involving brain or hepatic angiotensinogen inhibitors, novel natriuretic peptides, aldosterone synthase inhibitors, and certain nonsteroidal mineralocorticoid receptor antagonists (such as esaxerenone and ocedurenone) have demonstrated efficacy in lowering both office and 24-hour ambulatory BP (Table 1). However, only a few preliminary studies have been conducted with these compounds so far. Therefore, their therapeutic efficacy and tolerability need to be confirmed through future long-term, randomized controlled clinical trials, comparing them with placebo and/or currently available antihypertensive drugs. As emphasized by recent guidelines, the goal of these studies is to improve BP control in the population using therapies that also enhance patient adherence to antihypertensive treatment.[47,48]

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How to Recognize Cardiac Amyloidosis: Clinical Case Explanation

Kardiyak Amiloidoz Nasıl Tanınır? Klinik Vaka Açıklaması

ABSTRACT

Cardiac amyloidosis is a rare systemic condition characterized by the extracellular accumulation of amyloid proteins in the heart. These proteins can be deposited in various cardiac structures, including the valves, endocardium, myocardium, and pericardium. This abnormal protein deposition can disrupt normal heart function, leading to a range of symptoms and complications, such as heart failure, arrhythmias, and even sudden cardiac death. The diagnosis of cardiac amyloidosis is typically suspected based on characteristic clinical features, electrocardiogram abnormalities, and echocardiographic findings, which prompt further evaluation and confirmation. We present the case of a 57-year-old woman hospitalized with significant exertional dyspnea, hypotension, lower extremity edema, and proteinuria. The aim of this case report is to enhance clinicians' understanding of this condition and to reduce the interval between symptom onset and diagnosis, thereby potentially improving the prognosis for affected patients.

Keywords: Amyloidosis, cardiovascular magnetic resonance, echocardiography, heart failure

ÖZET

Kardiyak Amiloidoz, kalp hücrelerinin dışına amiloid proteinlerinin birikmesiyle seyreden nadir görülen bir durumdur. Bu proteinler kalp kapakları, endokard, miyokard ve perikard gibi kalbin farklı bölgelerinde birikme eğilimindedir. Bu anormal protein birikimi, kalbin normal fonksiyonunu bozarak kalp yetmezliği, aritmiler ve hatta ani kalp ölümlerine neden olabilir. Kardiyak amiloidoz tanısı, ileri değerlendirme ve doğrulama gerektiren karakteristik bulgulara, elektrokardiyografi anormalliklerine ve ekokardiyografik özelliklere dayanarak şüphelenilir. Sunulan vakada, 57 yaşındaki bir kadın hasta ciddi efor dispnesi, hipotansiyon, alt ekstremite ödemleri ve proteinüri semptomlarıyla hastanemize yatırılmıştır. Bu vaka sunumunun amacı, hekimlerin bu durumun farkındalığını artırmak, semptomların başlamasından teşhise kadar geçen süreyi azaltmak ve böylece hastaların prognozunu iyileştirmektir.

Anahtar Kelimeler: Amiloidoz, kardiyovasküler manyetik rezonans, ekokardiyografi, kalp yetmezliği

CASE REPORT
OLGU SUNUMU

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Amyloidosis is a rare disease characterized by the extracellular deposition of fibrillar proteins, which disrupt normal tissue architecture.[1] Amyloid deposits can affect multiple organs, including the heart, kidneys, liver, and gastrointestinal tract, with specific manifestations depending on the type of amyloidosis. Cardiac amyloidosis (CA) is notable for its rapid progression to heart failure.[2] The two most common types affecting the heart are immunoglobulin light chain amyloidosis (AL-CA) and transthyretin amyloidosis (ATTR). With an aging population, the prevalence of ATTR-CA is expected to rise. However, it is often underdiagnosed due to its slow progression and the non-specific nature of symptoms in older adults.[3]

Early and accurate identification of the CA subtype is essential for optimal patient management. Patients presenting with a hypertrophic cardiac pattern and heart failure with preserved ejection fraction (HFpEF), especially those who do not respond adequately to diuretic therapy, should be evaluated for infiltrative or storage diseases. CA is frequently diagnosed in this subset of patients.

Case Report

A 57-year-old woman was admitted to the clinic with significant weakness, hypotension, exertional dyspnea, and ankle swelling. She had been receiving optimal

medical therapy for congestive heart failure for the past two years, but her symptoms had progressively worsened over the previous three months (New York Heart Association (NYHA) Functional Classification Class III to IV). A chest X-ray revealed massive bilateral pleural effusion, necessitating pleural drainage on both sides. Despite high-dose loop diuretic therapy during this period, peripheral edema persisted. Auscultation revealed absent breath sounds bilaterally at the lung bases, arrhythmic heart sounds, and a midsystolic murmur in the mitral area. Her blood pressure was 90/55 mmHg, pulse rate 85 beats per minute, and oxygen saturation was 94% on room air.

The electrocardiogram (ECG) showed low-voltage QRS complexes in the limb leads and atrial fibrillation (Figure 1). Transthoracic echocardiography (TTE) revealed mildly reduced left ventricular ejection fraction (LVEF = 50%), concentric left ventricular hypertrophy, particularly of the interventricular septum (IVS 16 mm), with the characteristic "granular sparkling" appearance of the myocardium (Figure 2A-C, Video). Additional findings included biatrial enlargement, grade III diastolic dysfunction (Figure 2D-E), increased right ventricular wall thickness (Figure 2F), elevated systolic pulmonary arterial pressure (45 mmHg), and a small pericardial effusion surrounding both ventricles (Figure 2A-C). Due to the inadequate response to diuretic therapy over three months, persistent bilateral pleural effusion, and marked shortness of breath, a thoracic computed tomography (CT) scan was performed. The CT confirmed bilateral pleural effusion (Figure 3). Laboratory analysis showed elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) (21,264 pg/mL; upper limit of normal: 225 pg/mL) and cardiac troponin I (514 ng/L; upper limit of normal: 19.8 ng/L). Total serum protein was low at 49.8 g/L

ABBREVIATIONS

AL-CA	Light chain amyloidosis
ATTR	Transthyretin amyloidosis
CA	Cardiac amyloidosis
ECV	Extracellular volume
HFpEF	Heart failure with preserved ejection fraction
LV	Left ventricle
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
RV	Right ventricular
TTE	Transthoracic echocardiography

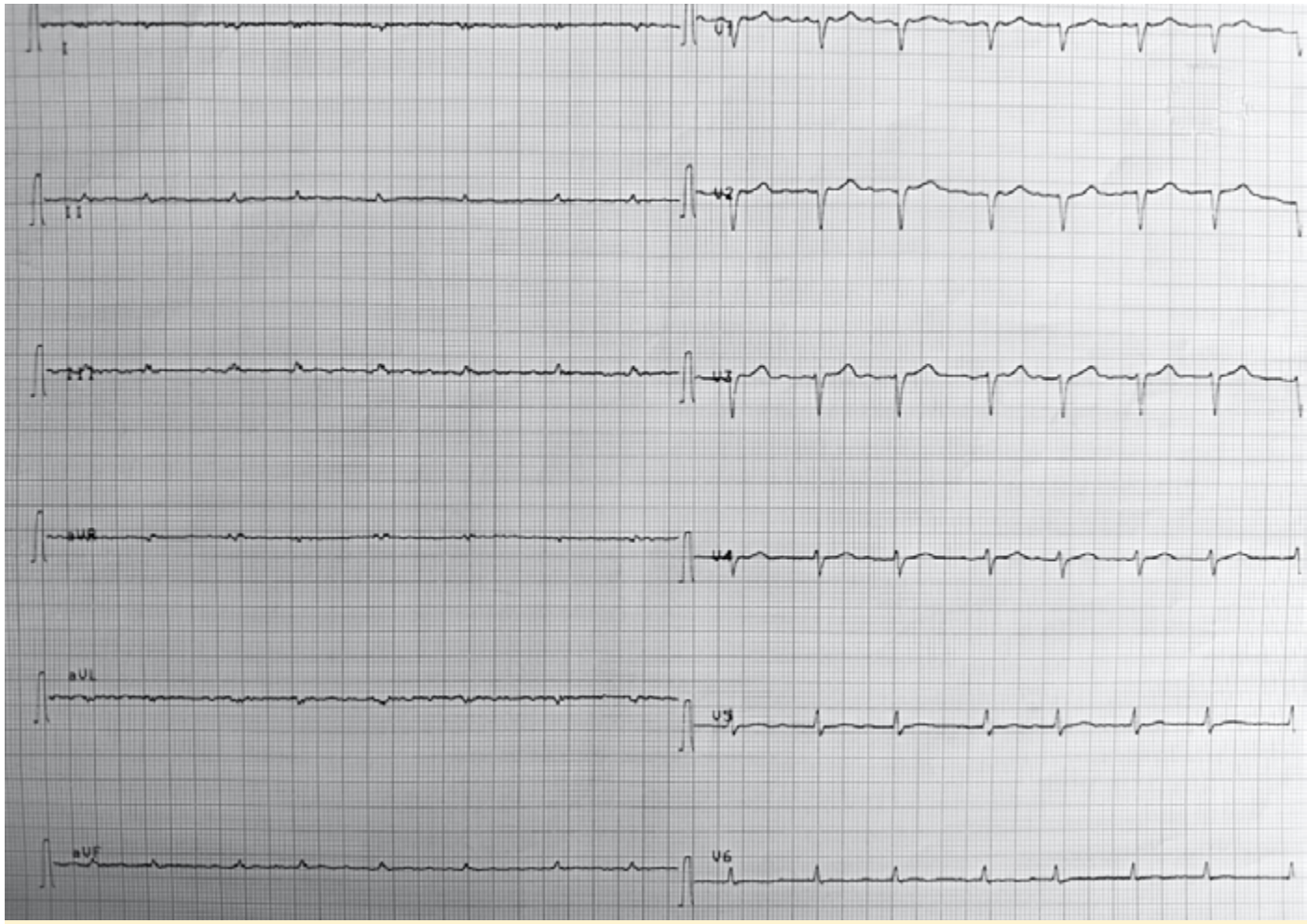

Figure 1. Electrocardiography.

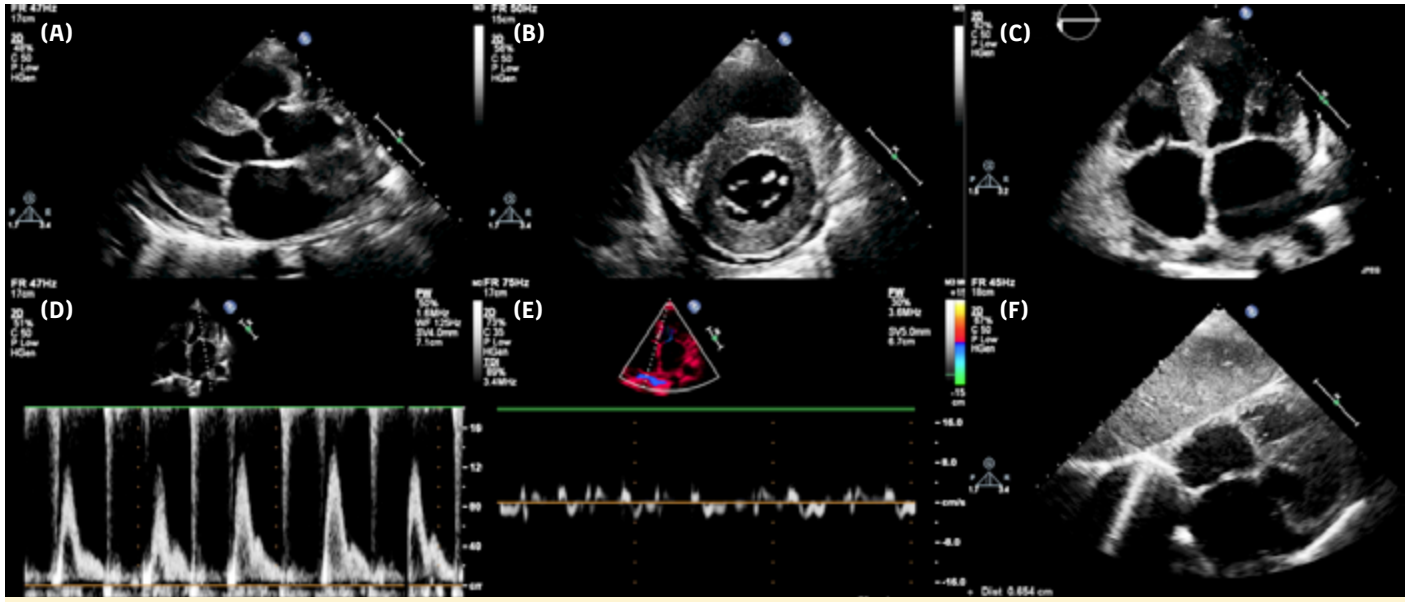

Figure 2. Echocardiography: (A) Parasternal long-axis view; (B) Parasternal short-axis view; (C) Apical four-chamber view; (D) Mitral inflow velocities; (E) Tissue doppler velocities; (F) Subcostal view.

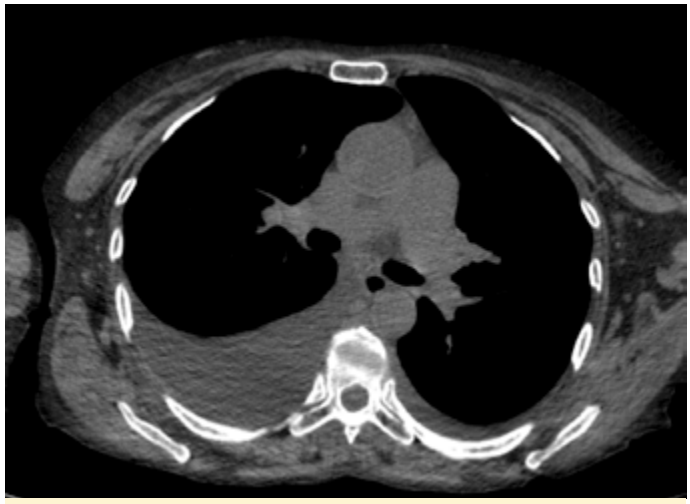

Figure 3. Computed tomography.

(normal lower limit: 64 g/L), and albumin was 2.2 g/dL (normal lower limit: 3.4 g/dL). Urine analysis revealed proteinuria (0.9 g/L). Other blood test results were within normal limits.

To clarify the etiology of the hypertrophied left ventricle (LV), the patient was referred for cardiac magnetic resonance imaging (MRI). MRI revealed predominant LV hypertrophy at the septal wall (17 mm) and mildly reduced LV systolic function (LVEF = 42%, left ventricular end-diastolic volume [LVEDV] = 56 mL/m^2, left ventricular end-systolic volume [LVESV] = 32 mL/m^2). Right ventricular (RV) wall thickness measured 6 mm. Mild biatrial dilatation was noted, along with the presence of fat tissue exhibiting a lipomatous appearance in the interatrial septum (IAS, 16 mm), a suggestive sign of CA (Figure 4A). A circumferential pericardial effusion with a thickness of up to 10 mm was also observed. Following gadolinium administration, patchy enhancement patterns

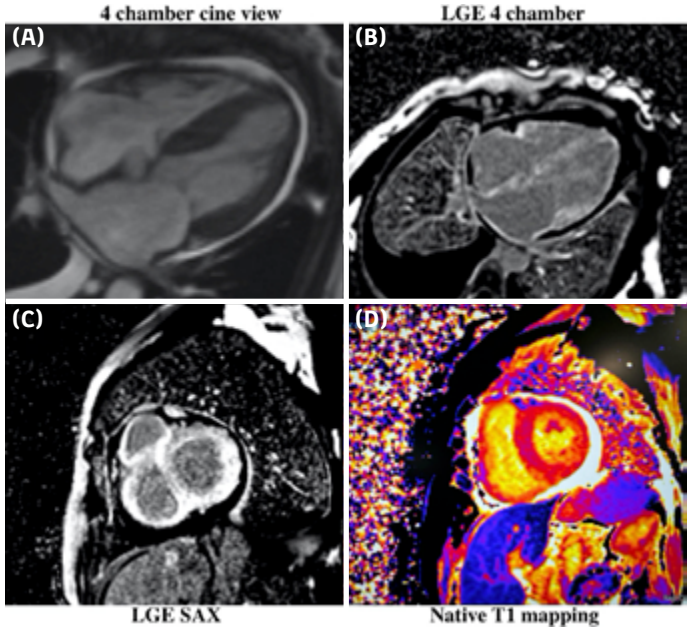

Figure 4. Cardiac magnetic resonance ımaging (MRI): (A) Apical four-chamber cine view; (B) Apical four-chamber late gadolinium enhancement (LGE) view; (C) Left ventricular (LV) short-axis late gadolinium enhancement (LGE) view; (D) Native T1 mapping.

were seen, with diffuse subendocardial and transmural involvement across all four chambers, including the interatrial septum (Figure 4B-C). Elevated native T1 mapping values (T1 mapping 1233 ms vs. reference 1040 ms) and increased extracellular volume (ECV, 37%) indicated extensive fibrosis (Figure 4D). These findings confirmed the diagnosis of CA. The patient was subsequently referred to a hematologist for further evaluation.

A bone marrow biopsy revealed hypercellularity with an increased count of kappa monotypic plasma cells and Congo red dye positivity, characteristic of amyloidosis. Multiple myeloma was ruled out due to normal blood immunoglobulin levels. Monoclonal light chains were detected in both serum and 24-hour urine samples by immunofixation electrophoresis: kappa chains were 3.07 g/L (normal range: 1.3–3.7 g/L) and lambda chains were 0.7 g/L (normal range: 0.93–2.42 mg/L). The kappa-to-lambda ratio was 4.20 (normal range: 1.17–2.93). An abnormal kappa-lambda ratio is observed in more than 90% of untreated cases of AL-CA. Based on these findings, the final diagnosis was light chain amyloidosis.

Following diagnosis, the patient was started on VRD therapy (bortezomib, lenalidomide, dexamethasone), along with supportive treatments including spironolactone, furosemide, rivaroxaban, and empagliflozin. Despite the initial chemotherapy sessions, clinical improvement was limited. Troponin I decreased to 398 ng/L and NT-proBNP to 19,789 pg/mL. Unfortunately, after three months of treatment, the patient showed no significant clinical improvement, likely due to the advanced stage of disease at the time of diagnosis. The patient passed away in the fourth month of treatment.

Table 1. Red Flags of Cardiac Amyloidosis

Red Flags	Presented in current patient
Heart failure	Yes
Aortic stenosis in ≥ 65 years	–
Hypotension or normotensive if previously hypertensive	Yes
Nefrotic syndrome	Yes
Peripheral or autonomic neuropathy	–
Bilateral carpal tunnel syndrome	–
Ruptured biceps tendon	–
Periorbital purpura	–
Decreased QRS voltage to mass ratio	Yes
Pseudo Q waves on ECG	–
Reduced longitudinal strain with apical sparing	–
Subendocardial/transmural LGE or increased ECV	Yes

ECG, Electrocardiogram; LGE, Late gadolinium enhancement; ECV, Extracellular volume.

Discussion

In AL amyloidosis, cardiac involvement occurs in up to 75% of cases.[3,4] AL-CA typically manifests after the age of 40 and shows no gender predisposition, whereas ATTR CA generally affects individuals over 65 years of age.[5] Median survival following diagnosis is approximately 24 months in AL-CA, compared to 31–69 months in ATTR amyloidosis. The presence of heart failure is associated with a poor prognosis, with a median survival of just six months, as seen in our case.[6] Due to its rarity and overlapping clinical features with other conditions such as chronic renal failure, hypertension, and hypertrophic cardiomyopathy, diagnosis of CA is often delayed, with an average diagnostic delay of around two years.

Recent advances in treatment have emphasized the importance of early diagnosis. Clinicians should be familiar with the diagnostic algorithm for CA to facilitate timely recognition. For example, patients with HFpEF who are refractory to diuretics should be evaluated for potential infiltrative or storage diseases, including CA. Diagnostic suspicion should be heightened in patients with LV wall thickening (>1 2 mm) and at least one associated 'red flag' symptom (Table 1).[6] Although our patient exhibited classic signs of AL-CA, achieving an early diagnosis remained a challenge.

ECG is a simple and routine diagnostic tool. In amyloidosis, typical ECG findings may include low-voltage ECG, a pseudoinfarction pattern, or atrial fibrillation. The next step in evaluation is TTE.

Basic and essential imaging techniques such as TTE are pivotal for both diagnosis and management. TTE serves as a fundamental tool, with characteristic features including biatrial enlargement, small hypertrophied ventricles, and pericardial effusion, findings suggestive of CA. LV wall thickening and a "speckled" myocardial appearance often indicate amyloid infiltration.[7] Marked LV hypertrophy (> 18 mm) tends to favor ATTR amyloidosis over AL amyloidosis.[8] LV systolic function is typically preserved or only mildly reduced. However, impaired global longitudinal strain parameters of the LV can be detected in early stages of the disease. An apical "sparing" pattern, specific to CA, may also be evident early on, along with diastolic dysfunction characterized by restrictive physiology.

In the presence of LV hypertrophy and a restrictive diastolic dysfunction pattern, cardiac MRI plays a key role in further tissue characterization. CA MRI is also valuable for monitoring treatment response in CA.[9] Late gadolinium enhancement (LGE) plays an important role in the diagnosis of CA. On LGE images, despite optimal imaging techniques, achieving proper myocardial nulling can be challenging. In CA, complete nulling of the myocardium occurs before the blood pool—an abnormal finding, as normally the myocardium nulls after the blood pool. This pattern has a high sensitivity (100%) and is strongly indicative of CA.[10] An increase in both native myocardial T1 relaxation time and ECV are also important diagnostic markers for CA.[11,12] The accumulation of amyloid fibrils in the myocardium leads to a diffusely increased ECV. As in our patient, diffuse hyperenhancement not only identifies cardiac involvement but also serves as a strong predictor of mortality.[13] The characteristic LGE pattern in CA is diffuse subendocardial enhancement, which has a specificity of 95%.[14] In some cases, diffuse transmural LGE may also be observed, typically in more advanced stages of the disease, and is associated with a particularly poor prognosis. The average 24-month survival rate is approximately 60% in patients with transmural enhancement, compared to 80% in those with subendocardial enhancement.[15] Our patient exhibited both transmural and subendocardial LGE involving all four cardiac chambers. Unfortunately, she survived only four months following diagnosis.

The findings for each form of amyloidosis vary depending on associated symptoms and diagnostic criteria. The most common symptoms of AL-CA include congestive heart

failure accompanied by nephrotic syndrome, macroglossia, orthostatic hypotension, and periorbital purpura (commonly referred to as "raccoon eyes"). In contrast, ATTR amyloidosis is more frequently observed in older adults (> 65 years) and is often associated with new-onset aortic stenosis, a history of carpal tunnel syndrome, or spinal stenosis. According to some studies, amyloid deposits in the ligamentum flavum have been found in approximately 40% of patients with lumbar spinal stenosis.[16] Studies indicate that low-voltage waveforms on ECG are more prevalent in the AL subtype compared to the ATTR subtype, although a pseudoinfarction pattern may be present in both. On TTE, concentric LV hypertrophy is more common in AL-CA, whereas eccentric LV hypertrophy is more typical of ATTR. Marked LV hypertrophy (> 18 mm) tends to favor a diagnosis of ATTR over AL amyloidosis. On cardiac MRI, diffuse transmural LGE is more commonly seen in ATTR amyloidosis compared to AL.

Based on the above diagnostic findings, CA was suspected. The next diagnostic step is to detect monoclonal light chains in the serum and 24-hour urine using immunofixation electrophoresis. The presence of monoclonal light chains in both serum and urine is indicative of AL-CA. In such cases, a biopsy of the involved organ is preferred to confirm the diagnosis. If no monoclonal proteins are detected in serum and urine, ATTR CA is more likely, and the subsequent step is to perform technetium-99m pyrophosphate ((99m)Tc-PYP) scintigraphy.

Endomyocardial biopsy is an invasive procedure that requires technical expertise and carries a risk of complications. In contrast, specific staining of bone marrow biopsy plays a crucial role in diagnosing AL-CA. Tissues stained with Congo red for amyloid appear pink and exhibit yellow-green birefringence under polarized light.[17]

In our case, the patient first underwent serum and urine immunofixation electrophoresis to detect monoclonal light chains (kappa and lambda). Given the extended turnaround time for these results (at least 10 days) and the patient's critical condition, we decided to perform a bone marrow biopsy simultaneously, based on the clinical presentation, non-invasive diagnostic findings, and a high probability of AL-CA, to expedite the diagnostic process.

Biomarkers such as troponin I and NT-proBNP play critical roles in both the diagnosis and prognosis of CA. In our case, NT-proBNP levels exceeding 8,500 ng/L indicated a very poor prognosis.[18,19]

Treatment of CA is complex and must be tailored to the specific amyloid type. Hypotension, which is especially common in AL-CA, often complicates standard heart failure therapies and requires careful management to avoid worsening hypotension. In advanced stages, beta-blockers are typically avoided, and treatment focuses on maintaining adequate cardiac output using diuretics and sodium-glucose co-transporter 2 (SGLT2) inhibitors.[20] The cornerstone of AL-CA treatment involves suppressing light chain production and promoting amyloid clearance, most commonly achieved through a regimen of cyclophosphamide, bortezomib, and dexamethasone (CyBorD).[21]

Diagnostic algorithm for cardiac amyloidosis is illustrated in Figure 5.

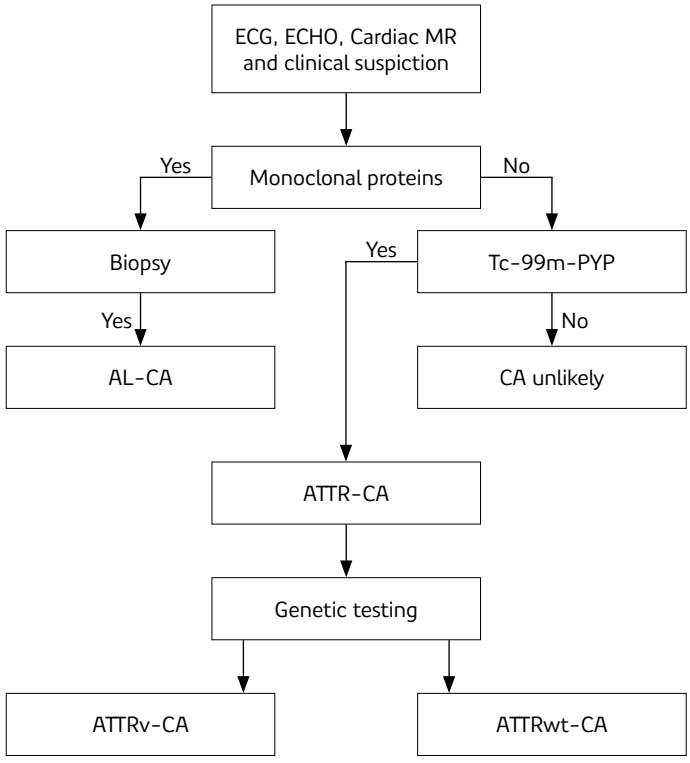

Figure 5. Diagnostic Algorithm for Cardiac Amyloidosis.

Conclusion

AL amyloidosis represents the most aggressive form of amyloidosis, particularly when diagnosed at an advanced stage. In our case, AL-CA presented with severe heart failure and extensive fibrosis involving all cardiac chambers, and was associated with a poor prognosis, with survival limited to six months. Amyloidosis remains a challenging condition to detect, often taking years from symptom onset to diagnosis. This clinical case underscores the importance of raising awareness among clinicians about this debilitating disease.

It is imperative to consider CA in patients with heart failure with preserved ejection fraction who are resistant to conventional therapies. Additionally, the presence of low-voltage findings on ECG combined with unexplained LV hypertrophy should raise suspicion of amyloidosis. Recognizing the "red flags" associated with the disease, such as elevated biomarker levels (NT-proBNP, troponin I), is essential for early diagnosis.

Non-invasive imaging modalities, including TTE and cardiac MRI, play pivotal roles in diagnosing CA, assessing disease severity, and guiding therapeutic strategies. Early identification and accurate classification of the amyloidosis subtype are critical for optimizing patient outcomes and implementing individualized treatment plans.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the participant for publication of this case.

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Peer-review: Externally/Internally peer-reviewed.

Video 1. Echocardiography: Apical 4 chamber view.

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Total Occlusion of the Infrarenal Aorta by Cardiac Myxoma: Emergent Surgical Management

İnfrarenal Aortun Kardiak Miksoma Nedeniyle Total Oklüzyonu: Acil Cerrahi Tedavi

ABSTRACT

Cardiac myxomas are the most common primary tumors of the heart and can cause systemic embolization, particularly when located in the left atrium. We present a rare case of a left atrial myxoma resulting in total occlusion of the infrarenal abdominal aorta. A 60-year-old man was admitted to the hospital with back pain, paresthesia in the lower extremities, and subsequent development of paraplegia. Computed tomography revealed total occlusion of the infrarenal aorta. Emergent surgery was performed, and the intraoperative specimen removed from the aorta was histologically identified as myxomatous material. Transthoracic echocardiography revealed a mass located in the left atrium. Despite a second surgery for the removal of the cardiac mass, embolic episodes caused by the myxoma could not be prevented. Prompt diagnosis and timely treatment are essential to improve clinical outcomes by preventing embolization-related complications.

Keywords: Abdominal aorta occlusion, atrial myxoma, cardiac mass, thromboembolism

ÖZET

Kardiyak miksomalar en sık görülen primer kalp tümörleridir ve sol atrial yerleşimli olduklarında sıklıkla sistemik emboliye neden olurlar. İnfrarenal abdominal aortun total tıkanıklığına neden olan nadir bir sol atriyal miksoma olgusunu sunuyoruz. 60 yaşında erkek hasta sırt ağrısı, alt ekstremitede parestezi ve ardından gelişen parapleji nedeniyle hastaneye başvurdu. Bilgisayarlı tomografide infrarenal aortun total oklüzyonu görüldü. Hasta acil cerrahiye alındı. Aorttan intraoperatif alınan örnegin histolojik olarak miksomatöz benzeri bir materyal olduğu tespit edildi. Hastaya yapılan transtorasik ekokardiyografide sol atriyum yerleşimli kitle saptandı. Kalp içi kitlenin çıkarıldığı ikinci cerrahiye ragmen, miksoma kaynaklı emboli atakları önlenemedi. Hızlı tanı ve dolayısıyla hızlı tedavi, embolizasyon kaynaklı komplikasyonları önleyerek klinik sonuçları iyileştirebilir.

Anahtar Kelimeler: Abdominal aort oklüzyonu, atriyal miksoma, kardiyak kitle, tromboembolizasyon

CASE REPORT
OLGU SUNUMU

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Myxomas are the most common primary tumors of the heart. Although their location can vary, they are most frequently found in the left atrium, typically attached to the atrial septum, with an incidence of 70–90%. It has also been reported in the literature that approximately 20% of cases can occur in the right atrium and about 5% in the left and right ventricles.[1] Although these tumors are histologically benign, they can lead to complications with a poor prognosis for the patient.[2]

Cardiac myxomas may present with obstructive, embolic, or constitutional symptoms. In addition, less common presentations include fever of unknown origin, endocarditis-like findings in the presence of infection, acute myocardial infarction, and pulmonary embolism. In some cases, the first symptom of a myxoma may be an embolic event, and the diagnosis of cardiac myxoma can be made through histopathological examination of embolic material removed from a peripheral artery.[1,3] When embolization occurs, the cerebral arteries are typically the most affected, followed by the renal artery, iliac artery, and femoropopliteal arteries. In rare cases, if the embolic myxoma material is particularly large, it can obstruct the infrarenal aortic bifurcation.[4] In this case report, we present a patient with cardiac myxoma who died due to a cerebral embolic event following surgery for infrarenal abdominal aortic embolism.

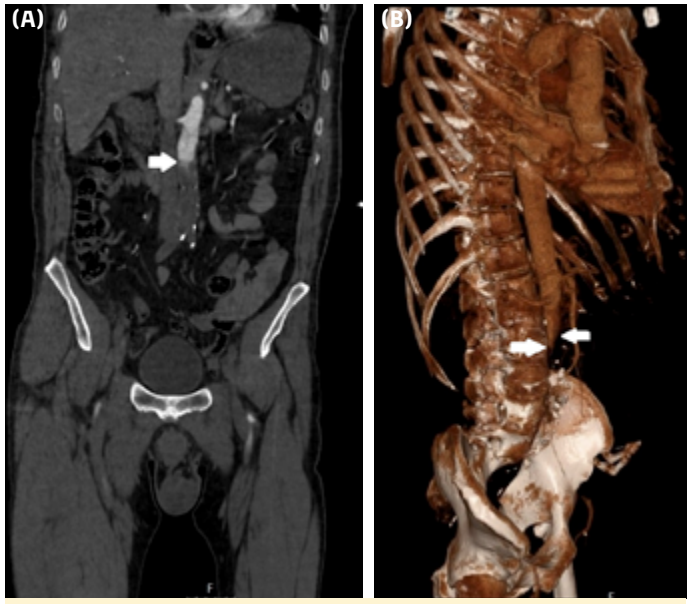

Figure 1. Computed tomographic angiography image showing total occlusion of the abdominal aorta, starting from the infrarenal level and extending to the bilateral femoral arteries (white arrow in A and B).

ABBREVIATIONS

ASD	Atrial septal defect
CT	Computed tomography
CTA	Computed tomographic angiography
ECG	Electrocardiography
GCS	Glasgow Coma Scale
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography

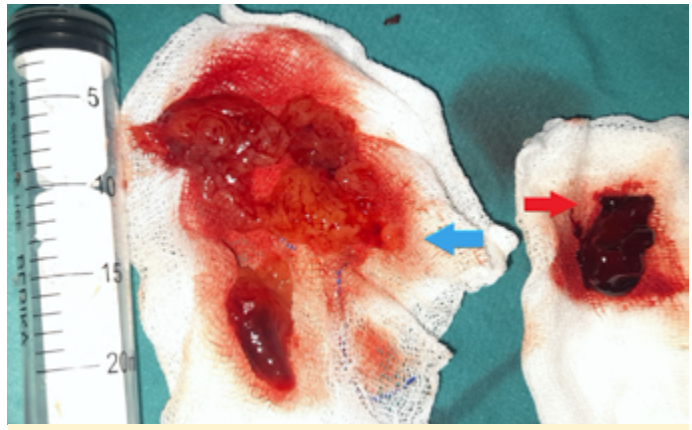

Figure 2. Embolectomy material with an irregularly shaped, solid, dirty beige myxoid appearance, measuring 2.7 × 2.5 × 1.5 cm and 1.8 × 1.6 × 1 cm, with some areas containing maroon-colored hemorrhage (marked with a blue arrow). A maroon-colored thrombus-like tissue fragment measuring 2.5 × 1.5 × 1.3 cm (marked with a red arrow).

Case Report

A 60-year-old male patient with no history of chronic disease presented to the emergency department with complaints of back pain, paresthesia in the lower extremities, and subsequent development of paraplegia. The absence of distal pulses prompted a consultation with the cardiovascular surgery team. Initial physical examination in the emergency department revealed a Glasgow Coma Scale (GCS) score of 15, clear consciousness, blood pressure of 170/90 mmHg in the upper arm, heart rate of 90 beats per minute, and a normal sinus rhythm on electrocardiography (ECG). Both lower extremities were cold, pale, and cyanotic. Computed tomographic angiography (CTA), performed prior to the consultation, showed occlusion of the aorta at the infrarenal level (Figure 1). The patient underwent emergent surgery, and thromboembolectomy was performed. During the procedure, the retrieved material was found to be gelatinous and soft in consistency (Figure 2). Postoperative physical examination revealed palpable femoral, popliteal, and distal pulses, with warming and improved coloration of the bilateral lower extremities.

The patient underwent cardiac computed tomography (CT), transthoracic echocardiography (TTE), and transesophageal echocardiography (TEE) to investigate the source of emboli and identify any additional embolic events. Cardiac CT revealed a thrombus-like mass approximately 4 cm in diameter located in the left atrium (Figure 3A), as well as renal infarcts in the upper and lower poles of the right kidney, and splenic infarcts in the lower pole of the spleen. Brain CT revealed a hypodense nodular lesion measuring 10 mm in the left parietal lobe and 7 mm in the right parietal lobe, both located at the level of the centrum semiovale. TTE showed a mobile mass in the left atrium with irregular borders, measuring 4 × 2 cm, along with second-degree mitral regurgitation. TEE demonstrated a mobile mass with irregular borders, measuring 4.8 × 1.8 cm, originating from the septal region of the left atrium (Figure 3B). The patient was urgently taken to surgery for removal of the intracardiac mass.

Surgical intervention was performed via median sternotomy under cardiopulmonary bypass with standard aortic and bicaval cannulation. A soft gelatinous mass measuring approximately 4.5 × 3 cm, occupying the left atrium and attached to the atrial septum, was accessed through left and right atriotomy incisions. A right atriotomy with a transseptal approach was performed to provide better access to the mass within the septal wall. An atrial septal defect (ASD) was created, the mass was completely excised, and the ASD was subsequently closed. The excised mass was sent for pathological examination (Figures 4, 5).

On the first postoperative day, the patient was awake, and the GCS score was 11. He responded to verbal stimuli but presented with left-sided hemiplegia. In addition to the preoperative cerebral infarct areas, control brain CT and magnetic resonance imaging showed (Figure 6) extensive acute diffusion restriction in the right hemisphere. The neurology team initiated treatment with enoxaparin sodium.

Despite medical management, brain death occurred during follow-up, and the patient was declared deceased on the fourth postoperative day.

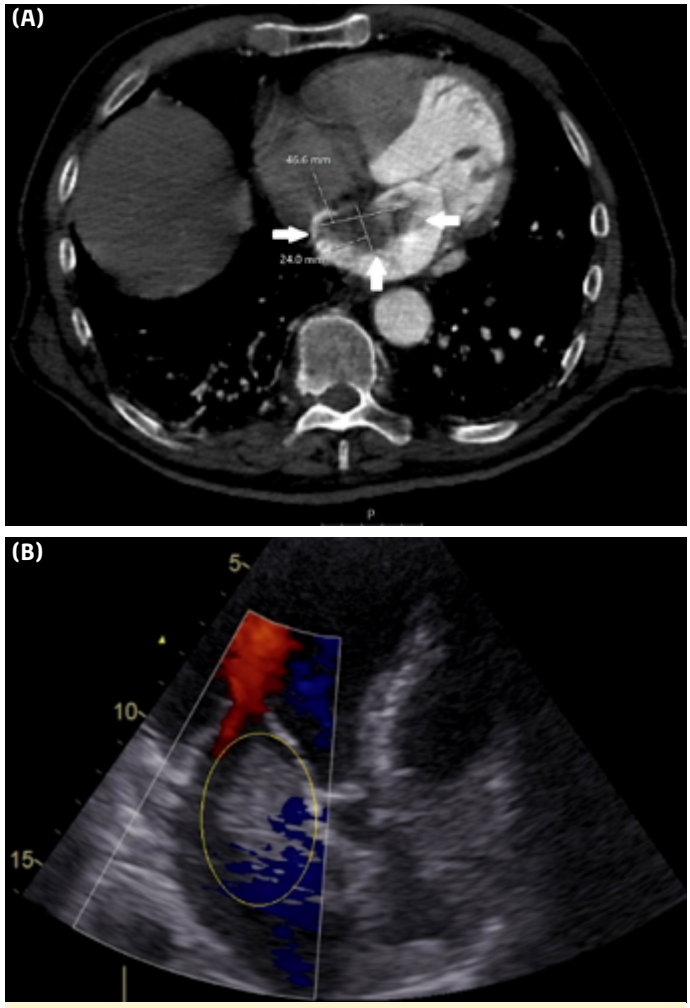

Figure 3. (A) Thoracic computed tomography image showing a thrombus-like mass approximately 4 cm in diameter in the left atrium (shown with white arrows in the axial section). (B) Transesophageal echocardiography image showing a mobile, irregularly bordered mass measuring 4.8 × 1.8 cm in the left atrium (circled in yellow).

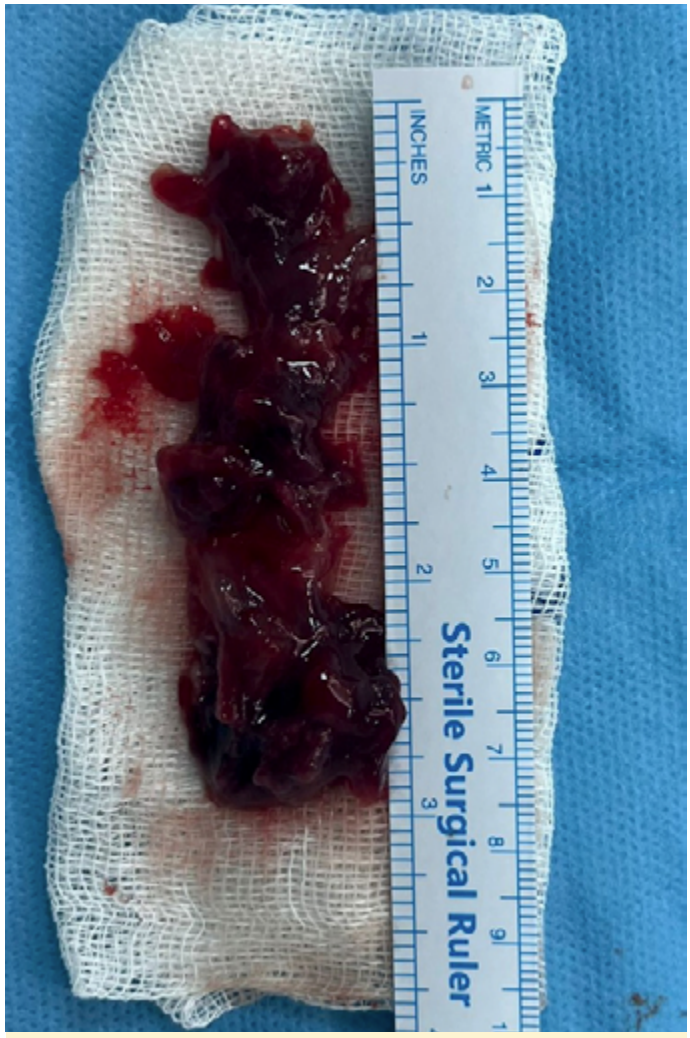

Figure 4. The mass removed from the left atrium measured 3 × 2.5 × 1.8 cm, and a smaller mass measured 1.1 × 0.8 × 0.2 cm. The majority of the tissues appeared maroon and hemorrhagic, with some areas showing beige-colored, soft-consistency myxoid features.

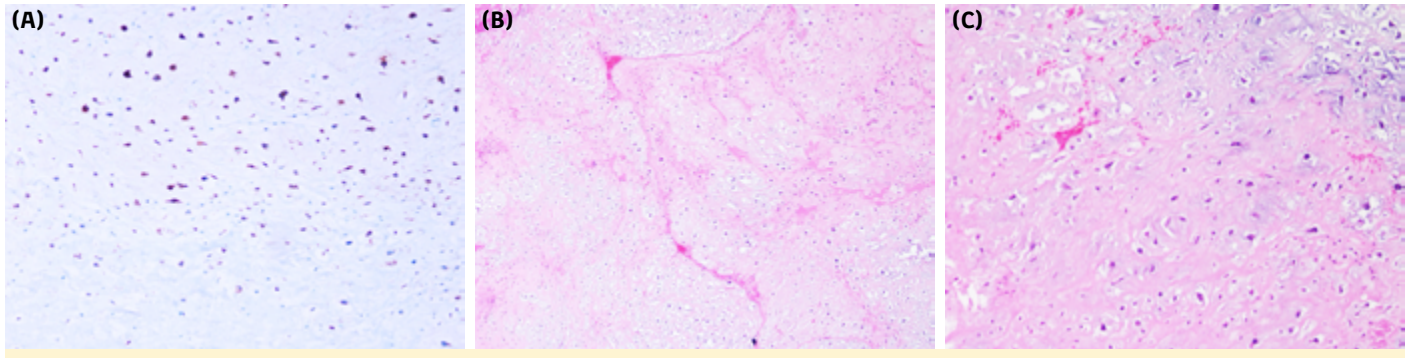

Figure 5. (A and B) Pathological specimen image showing stellate-shaped stromal cells in a myxoid, vascular-rich stroma (x100, hematoxylin-eosin staining). (C) Pathological specimen image showing CD34 positivity in stromal cells (x40, immunoperoxidase staining).

Discussion

Myxomas may present clinically with nonspecific symptoms such as weakness, fever, weight loss, and myalgia, in addition to symptoms related to obstruction within the heart or cerebral and peripheral embolization.[5] In more than 50% of cases, myxomas are diagnosed only after systemic embolization or

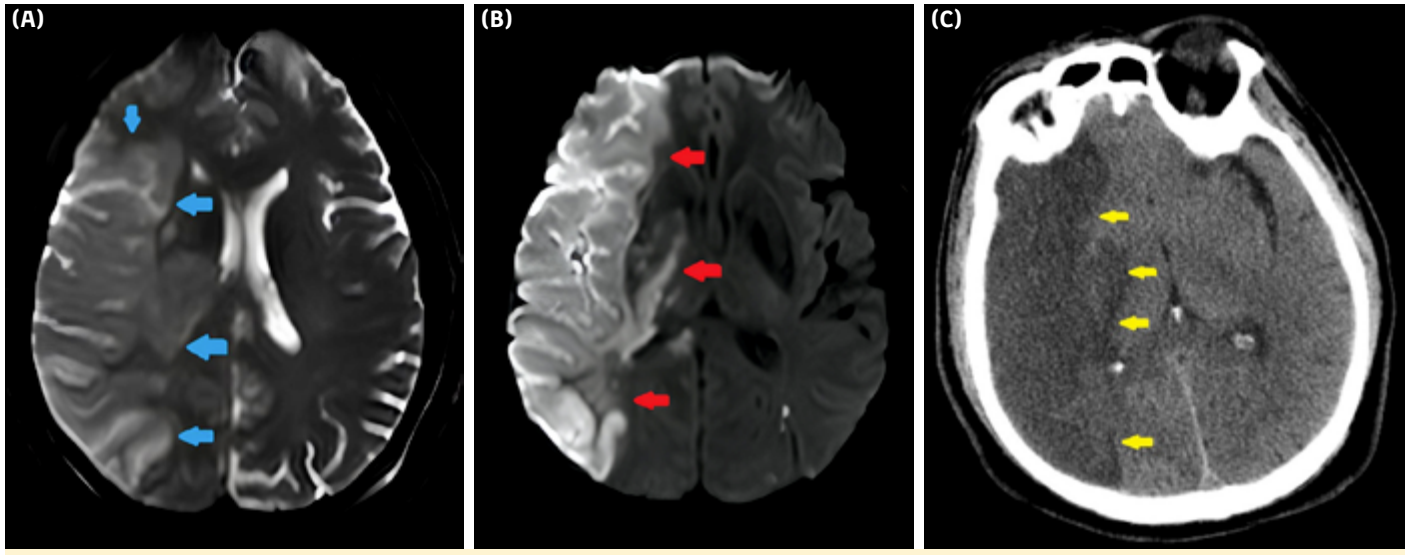

Figure 6. (A and B) Magnetic resonance images taken on postoperative day 1 (blue and red arrows): Diffuse diffusion restrictions in the region corresponding to the right middle cerebral artery (MCA) territory; additional diffusion limitations in the bilateral lateral ventricles, left frontobasal region, left occipital lobe, and bilateral cerebellar hemispheres. (C) Computed tomography image (yellow arrows): Diffuse hypodense areas in the right cerebral hemisphere consistent with the MCA territory, along with localized hypodense areas in the left cerebellar hemisphere.

when the tumor reaches a size that obstructs the heart valves and causes hemodynamic disturbances. Systemic embolism is the most significant complication of myxomas located in the left atrium.[1,3]

The typical location for myxomas is the fossa ovalis in the interatrial septum. The cardiac chamber in which the mass is located and the surface to which it is attached provide important clues for differentiating myxomas from thrombi, vegetations, and other tumors. In this distinction, the patient's clinical presentation, along with TTE and TEE findings, play a critical role.[1,3] In our case, the myxoma was localized in the left atrium and had caused embolic events in multiple organs. Once the diagnosis of cardiac myxoma is established, surgical excision should be performed as soon as possible, given the ongoing risk of embolic complications. Careful handling of cardiac structures and the tumor during removal reduces the risk of intraoperative embolic events as well as the likelihood of tumor fragmentation.[2]

Macroscopically, if the tumor is soft, villous, and has papillary projections, it is more prone to embolization. In contrast, tumors with a smooth and more fibrotic surface are less likely to cause embolization. Myxomas localized in the right atrium more frequently exhibit calcification and, as a result, are reported to cause fewer embolic events. Embolism occurring in the absence of cardiac arrhythmia is considered characteristic of myxomas.[6] In our case, the thrombectomy material was macroscopically soft, easily fragmentable, and had an irregular surface. The patient did not have any cardiac arrhythmia.

Left atrial myxomas are a rare but recognized cause of stroke and acute limb ischemia.[6]

Tumor cells seeded within the embolus may proliferate and form metastatic lesions.[7] Emboli most commonly affect the brain but may also involve other organs, such as the liver, spleen, kidneys, retina, coronary arteries, and peripheral arteries.[8] In rare cases, a left atrial myxoma may completely detach and obstruct the aortic bifurcation. Emboli of this size at the aortic bifurcation have been reported in the literature to mimic the clinical presentation of aortic dissection and may require immediate surgical intervention.[8,9] It is generally recommended to remove the primary cardiac lesion before addressing brain metastases, unless there are urgent surgical indications, such as hemorrhage with significant mass effect or progressive neurological deficits.[7] There have been reports of cases where myxoma emboli manifest as systemic or cerebral metastases, even years after removal of the cardiac tumor, as well as cases of pulmonary hypertension when the tumor originates from the right atrium.[7,10] Due to the rarity of metastatic myxomatous lesions, data on their treatment are limited, and there are no established standards of care.[7] Early diagnosis is crucial, as it significantly reduces complications related to arterial occlusion and increases survival rates.

In our case, peripheral embolizations occurred in the splenic artery, renal artery, cerebral arteries, and abdominal aorta. Despite prompt intervention with embolectomy and atrial myxoma removal, the development of extensive peripheral organ emboli in the preoperative period ultimately led to mortality in this case.

Conclusion

In patients presenting with sudden arterial embolism and no prior medical history, cardiac myxoma should be suspected, particularly in the absence of cardiac arrhythmia, atherosclerosis, or previous thromboembolic events. In cases of embolization affecting multiple regions, intracardiac masses, especially myxomas, should be considered in the differential diagnosis. Prompt diagnosis and timely treatment are essential to improve clinical outcomes and prevent embolization-related complications.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient and his relatives.

Conflict of Interest: The authors declare no conflict of interest.

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Author Contributions: Concept – R.Ö., A.T.,Ş.Ç.,G.S.; Design – R.Ö., A.T., Ş.Ç.,G.S.; Supervision – Ş.Ç., G.S.,R.Ö.; Resource – Ş.Ç., G.S.,R.Ö.; Materials – Ş.Ç., R.Ö., A.T., G.S., Ö.C.; Data Collection and/or Processing - Ş.Ç., R.Ö.,G.S., Ö.C., N.H.; Analysis and/or Interpretation - Ş.Ç., R.Ö., G.S.; Literature Review – Ş.Ç., G.S.,R.Ö.; Writing – Ş.Ç.; Critical Review – Ş.Ç., R.Ö.

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Entrapment of a Multipolar Mapping Catheter in a Mitral Valve Prosthesis

Mitral Kapak Protezinde Çok Kutuplu Haritalama Kateterinin Tuzaklanması

CASE IMAGE
OLGU GÖRÜNTÜSÜ

Electroanatomic mapping is crucial in the ablation of complex atrial arrhythmias. The PentaRay® NAV eco catheter (Biosense Webster, CA, USA), featuring five flexible splines embedded with microelectrodes, offers high-resolution mapping but poses a risk of entrapment in mechanical mitral valves, due to its multi-spline design.

We report the case of a 74-year-old woman with coronary artery disease, prior coronary artery bypass grafting (CABG) and mechanical mitral valve replacement, who was referred for atrial fibrillation ablation. During mapping with a PentaRay catheter near the posteroinferior mitral annulus, resistance was encountered. Cine fluoroscopy revealed entrapment of a spline in the valve, resulting in leaflet obstruction and hemodynamic instability. Manual manoeuvres—including counterclockwise rotation of the PentaRay hub and advancement or withdrawal of the sheath over the catheter shaft—failed to release the catheter. It was eventually withdrawn with force (Videos 1 and 2), which restored valve function but caused rupture of a spline (Video 1, Figures 1 and 2). The ruptured fragment embolized while preparations were underway to retrieve it with a snare. Fluoroscopy localized the embolized fragment in the left hemithorax. Angiography ruled out pulmonary embolization, suggesting localization within the thoracic vasculature (Video 1). Echocardiography confirmed normal valve function. The procedure concluded without further complications and the patient was discharged after 48 hours of observation. Follow-up imaging later identified the fragment in a distal intercostal artery (Figure 2, Video 3).

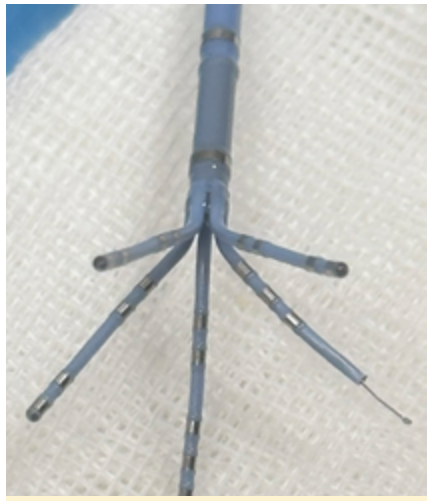

Figure 1. Ex-vivo catheter image showing four normal splines and one ruptured spline.

Intra-procedural best practices include avoiding direct catheter advancement toward the mitral orifice, using long steerable sheaths for better control, employing real-time multi-view fluoroscopy or echocardiography and considering single-tip or single-spline catheters, or high-density basket catheters, when appropriate. Time spent near high-risk areas such as the posterior mitral annulus should be minimized. Electroanatomic systems with valve contouring and intracardiac echocardiography can further enhance procedural safety.

If entrapment occurs, initial management should prioritize hemodynamic stability and cessation of all catheter manipulation. Gentle sheath advancement or catheter rotation under imaging guidance may resolve the entrapment. Forceful withdrawal should be a last resort, particularly in the setting of hemodynamic compromise. It is essential that electrophysiology lab staff are trained to recognize and respond promptly to catheter entrapment scenarios.

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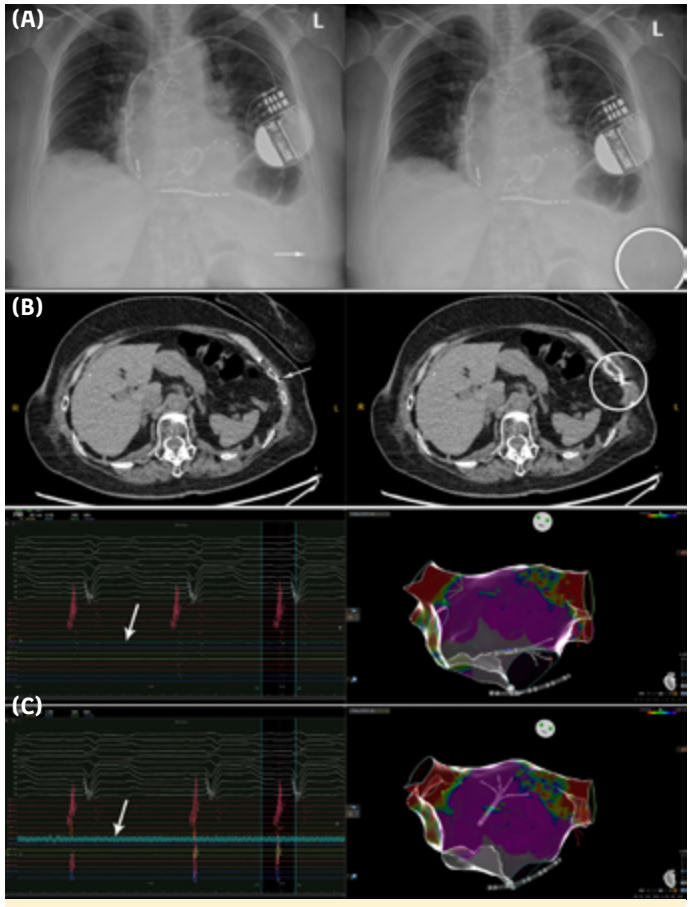

Figure 2. Teleradiograph showing the embolized segment (arrow) near the distal left rib cage in normal (left) and magnified (right) images (A). Computed tomography showing the embolized segment (arrow) in the distal portion of the intercostal artery in normal (left) and magnified (right) axial images. 3D mapping showing all five splines, with at least one located at the orifice of the mechanical valve and far-field atrial and ventricular signals on intracardiac electrograms (arrow) (upper). 3D mapping showing four splines in the left atrial cavity and continuous artifact recording in bipole 5-6 (arrow), with normal electrograms in the remaining electrodes (lower).

This case highlights a rare but potentially life-threatening complication associated with the PentaRay catheter in patients with mechanical mitral valves. Preventive imaging and meticulous procedural planning are critical. A structured retrieval strategy may eliminate the need for surgical intervention and ensure patient safety.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: The patient provided written informed consent for the publication of this case report and any accompanying images. All identifiable information has been anonymized to protect patient privacy.

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Video 1. Fluoroscopic images demonstrating PentaRay entrapment in the mechanical mitral valve, attempts at release, subsequent rupture and embolization of a spline (arrows), and angiography for embolized segment localization (PA, Pulmonary artery; PV, Pulmonary vein).

Video 2. 3D mapping showing five splines with at least one at the valve orifice, and far-field atrial and ventricular signals without artifact on intracardiac electrograms (arrowheads) (upper) and, 3D mapping showing four splines in the left atrial cavity, with continuous artifact recording in bipole 5-6 (arrowheads), while the other electrodes show normal electrograms (lower).

Video 3. Serial computed tomography images showing the embolized segment (arrows) to the intercostal artery, at the posterior aspect of the left distal rib cage, in axial (left) and sagittal (right) views.

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A Journey from Vertebra to Pulmonary Artery: The Silent Threat of Pulmonary Cement Embolism Following Vertebroplasty

Vertebradan Pulmoner Artere Yolculuk, Vertebroplasti Sonrası Sement Embolisinin Sessiz Tehdidi

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 76-year-old female patient presented to the cardiology clinic with complaints of dyspnoea, palpitations and irregular blood pressure. New-onset dyspnoea limiting exertional capacity was present. She had a history of hypertension and underwent percutaneous vertebroplasty for vertebral compression fractures fifteen years ago. On initial examination, the electrocardiogram (ECG) showed sinus rhythm. An echocardiography revealed a normal ejection fraction, mild tricuspid regurgitation and systolic pulmonary artery pressure of 33 mmHg. Both the right atrium and right ventricle appeared normal and laboratory tests for Troponin I and BNP were within normal limits. The D-dimer level was measured at 0.67 mg/L.

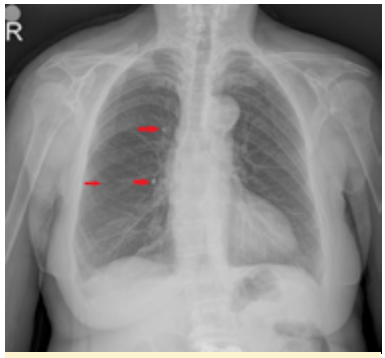

Figure 1. Chest X-ray, pulmonary cement pieces and vertebroplasty materials in L3 vertebral body.

Chest X-ray showed linear and nodular opacities in the right lung, in addition to material from the previous vertebroplasty procedure (Figure 1). A computed tomography (CT) angiography was subsequently performed, which identified

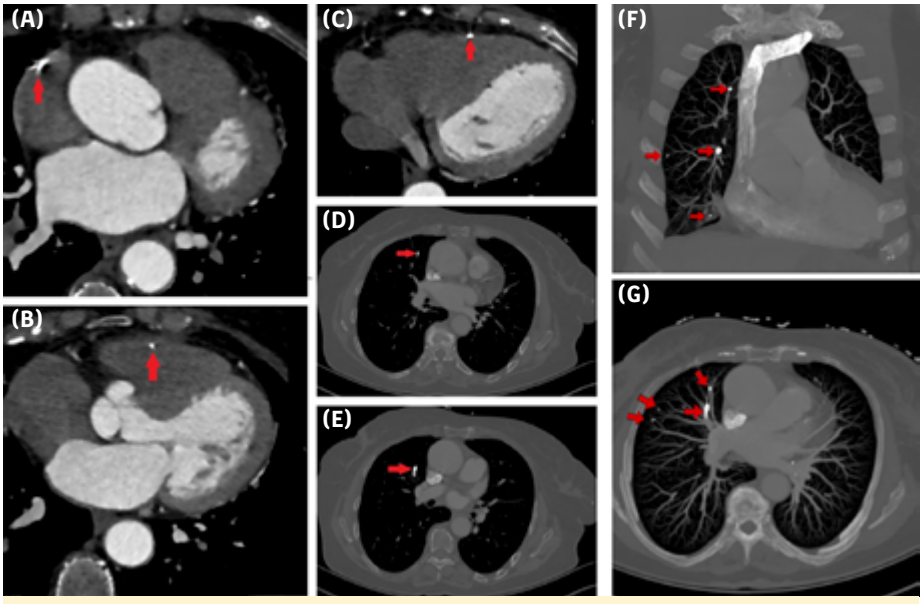

Figure 2. Cardiac and Pulmonary CT, arrows demonstrate multiple hyperdense foci compatible with cement embolism. (A) Right atrial cement pieces, (B, C) Right ventricular cement pieces, (D, E) Pulmonary cement embolism, (F, G) Axial and coronal bone window MIP images.

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multiple millimetric radio-dense materials in the right atrium, right ventricle and segmental pulmonary arteries, suggestive of pulmonary cement embolism (PCE) (Figure 2).

Following the identification of PCE, antihypertensive therapy and anticoagulant treatment were initiated, leading to significant improvement in the patient's symptoms. The diagnosis of PCE was made incidentally while investigating cardiac aetiology in a patient with dyspnoea.

Given the increased operative risks associated with vertebral fractures in elderly patients, percutaneous vertebroplasty is commonly preferred. Cement particles can extravasate from the paravertebral space into the venous system, traveling through the vertebral venous plexus and then into the azygos venous system. From there, they drain into the superior vena cava, right heart and eventually the pulmonary arteries, facilitated by the lack of valves in the vertebral venous system.

Although rare, PCE can be life-threatening. Clinical manifestations can range from local compression to progressive embolization and may mimic conditions such as coronary artery disease, pulmonary embolism or heart failure. Symptoms may include chest pain, dyspnea, tachypnea, or in severe cases, hypoxia, hypotension, arrhythmias and cardiac arrest. The presence of cement particles in the right heart can lead to serious complications, such as cardiac rupture and tamponade.

PCE may present shortly after the surgery or may develop after a long period of time. It can be classified as central and peripheral according to the location and as symptomatic and asymptomatic according to the clinic. When the literature is reviewed, it can be seen that there is no consensus in terms of treatment for PCE. In general, no additional treatment is recommended in asymptomatic patients with peripheral embolism and clinical follow-up is recommended. Anticoagulation is recommended in patients with symptomatic peripheral embolism and in the group with central embolism. Anticoagulation with Coumadin is generally recommended for 3 to 6 months.

Therefore, PCE should be considered in the differential diagnosis of patients with a history of vertebroplasty and relevant symptoms. Chest X-ray findings of linear opacities in such cases should prompt further investigation with CT angiography and echocardiography should be planned for a comprehensive cardiac evaluation.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Artificial Intelligence in Cardiac Rehabilitation: Assessing ChatGPT's Knowledge and Clinical Scenario Responses

Kardiyak Rehabilitasyonda Yapay Zeka: ChatGPT'nin Bilgi Düzeyinin ve Klinik Senaryo Yanıtlarının Değerlendirilmesi

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

I read the article by Geneş et al.[1] with great interest, as it presents a well-organized and insightful analysis of a subject that is becoming increasingly significant in the field. In this context, I would like to present a few complementary remarks that may deepen the appreciation of the study's relevance and applicability.

Artificial intelligence (AI) has been increasingly employed to advance various domains of patient care, including the management of electronic health records, the development of personalized treatment strategies and diagnostic imaging interpretation.[2] If proven to be both reliable and intelligible, such tools have the potential to function as meaningful adjuncts to clinical practice, enhancing the quality of clinical decision-making, while concurrently promoting patient adherence and engagement within the framework of cardiovascular rehabilitation (CR).[3] Several studies have evaluated the responses of ChatGPT to common patient and clinician questions related to prevalent cardiovascular conditions, including heart failure, coronary artery disease, hypertension, hyperlipidemia and atrial fibrillation.[4-8] It has been observed that ChatGPT-4o's responses to general and clinical scenario-based questions related to CR are largely consistent with current clinical guidelines.[1] Although a previous study reported that users found tools such as Copilot or Gemini to be more user-friendly than ChatGPT when seeking health-related information, it is important to note that this comparison was based on an earlier version, specifically ChatGPT-3.5.[9] Given the considerable improvements in more recent versions, such as GPT-4 and GPT-4o, notably in clinical reasoning, contextual accuracy and guideline adherence, the findings of that study may not be generalizable to current AI capabilities. Its explanations on core topics such as multidisciplinary team approaches, risk stratification and principles of exercise prescription, are user-friendly and easy to understand. However, there are limitations to its current capabilities. For instance, ChatGPT-4o's responses regarding high-intensity interval training and resistance exercises for elderly or frail individuals lack depth. Additionally, the model shows gaps in more complex areas, such as pharmacological therapies and metabolic disorders, limiting its ability to provide comprehensive clinical evaluations. Moreover, there is insufficient explanation regarding technical parameters used to determine exercise intensity (e.g., %HRR, METs, VO_2peak and watt values), which highlights a gap between theoretical knowledge and practical application. Despite these limitations, ChatGPT-4o operates without accessing personal data and emphasizes the importance of consulting professional healthcare providers, demonstrating its ethical responsibility.

This study conducted an evaluation based on a limited pool of scenarios and questions, which restricts the generalizability of its findings. Furthermore, the model's impact on patient outcomes, clinician workload or patient satisfaction was not assessed. More comprehensive regulations are needed in areas such as algorithm transparency, data security, ethical standards and cultural adaptability. Additionally, it is crucial that the data used to train these algorithms be representative and free from bias in order to promote equity in healthcare delivery. In conclusion, the findings of the present study suggest that AI-based systems, such as ChatGPT-4o, hold promise as supplementary tools in complex clinical domains, including cardiac rehabilitation, by offering guideline-consistent information and supporting multidisciplinary decision-making processes.

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Reply to Letter to the Editor: Artificial Intelligence in Cardiac Rehabilitation: Evaluating ChatGPT's Knowledge Level and Responses to Clinical Scenarios

Editöre Mektup Yanıtı: Kardiyak Rehabilitasyonda Yapay Zeka – ChatGPT'nin Bilgi Düzeyi ve Klinik Senaryolara Yanıtlarının Değerlendirilmesi

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

To the Editor,

We have read with great interest the valuable commentary[1] on our article entitled "Artificial Intelligence in Cardiac Rehabilitation: Evaluation of ChatGPT's Knowledge Level and Responses to Clinical Scenarios.[2] We are grateful for these constructive contributions regarding the evolving role of artificial intelligence (AI) in cardiovascular medicine. On this occasion, as researchers in AI and cardiology, we would like to further clarify our perspective and elaborate on several key points in greater depth.

First and foremost, we would like to highlight a noteworthy finding of our study. Although ChatGPT is a general-purpose conversational agent that was not specifically designed to address the complex and specialized requirements of healthcare, it demonstrated remarkable accuracy within a highly specific subspecialty of cardiology, such as cardiac rehabilitation. Importantly, we did not observe any overt misinformation in its responses: the limitations we identified were primarily related to a lack of detailed elaboration on highly specialized topics, rather than to incorrect or misleading guidance. The ability of a general AI model to perform at this level in a domain requiring up-to-date, expert knowledge based on current guidelines, in our view, strongly underscores the significant—yet still largely unrealized—potential of such technologies to support healthcare delivery. Indeed, one of the central aims of our study was to shed light on this important and emerging capacity of artificial intelligence.

Secondly, we believe that the comparative benchmarks used to evaluate AI tools in medical research should be carefully considered. There is a tendency to assess AI performance against an absolute and comprehensive standard of knowledge. However, we argue that a more pragmatic and clinically meaningful benchmark is often the performance of human experts. Indeed, numerous studies have demonstrated that AI can achieve high levels of accuracy when compared to human specialists.[3] In our study, the 40 questions we posed (20 based on general principles, 20 on clinical scenarios), were specifically designed to reflect the core principles of cardiac rehabilitation. Notably, ChatGPT-4o demonstrated a high degree of concordance with current clinical guidelines. To place this in context, in many academic and professional settings where human expertise is assessed, a correct response rate of approximately 60–70% on comparable questions is generally regarded as the threshold for competence. Of course, this metric alone is not an absolute criterion for clinical proficiency, but it is widely recognized as an important indicator in the evaluation of clinical knowledge and practical skills. From this perspective, the performance exhibited by current AI models suggests significant potential to serve as supportive and empowering tools for clinicians, rather than outright replacements in clinical decision-making processes. Thus, the integration of AI-based systems into healthcare represents a substantial opportunity to enhance the quality of clinical practice and optimize patient care, through increased collaboration between humans and technology.

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While artificial intelligence (AI) applications in medicine hold great promise, they also raise significant ethical, technical and legal concerns. Foremost among these is the issue of systematic bias embedded within the datasets used to train AI models, which often reflect underlying societal inequalities. Such biases carry the risk of producing outcomes that disadvantage certain demographic groups, thereby exacerbating existing health disparities.[4] Additionally, the "black box" nature of many deep learning models frequently limits the ability of clinicians to fully understand the rationale behind AI-generated diagnoses or treatment recommendations.[5] This underscores the need for greater algorithmic transparency. Key unresolved issues also include the allocation of legal and ethical responsibility in the case of erroneous AI outputs (whether this liability lies with the developer, institution or clinician), the safeguarding of patient data privacy and the risk that clinicians may become overly reliant on AI systems, potentially diminishing their own clinical skills.[6] In this context, the safe and equitable integration of AI into clinical practice requires not only technological advancements, but also rigorous validation procedures, transparency and the establishment of robust, human-centered regulatory frameworks.[7]

We concur that the integration of AI into routine clinical care remains an ongoing process that brings with it numerous questions, requiring further investigation. Areas such as the impact of AI on patient satisfaction, its effectiveness across patient groups with diverse socio-cultural and economic backgrounds and strategies for optimal integration into existing clinical workflows, should be prioritized in future research. The outcomes of such studies will provide a foundation for more equitable, effective and patient-centered applications of AI in healthcare.

In conclusion, while acknowledging the current limitations of AI models, it is essential to emphasize the need for continuous development, robust regulatory frameworks and rigorous ethical oversight. Advanced AI systems such as ChatGPT-4o offer clinicians valuable supportive tools in complex clinical domains like cardiac rehabilitation, by providing information aligned with clinical guidelines and facilitating multidisciplinary decision-making processes. Our ultimate goal is to enhance the quality of healthcare services and optimize patient care.

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Uric Acid/Albumin Ratio: Beyond Risk Stratification to Therapeutic Guidance in Hypertension

Ürik Asit/Albümin Oranı: Hipertansiyonda Risk Sınıflandırmasının Ötesinde Tedaviye Yön Veren Bir Parametre

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

We read with great interest the study by Karayiğit et al.,[1] titled "The Correlation Between Serum Uric Acid/Albumin Ratio and Circadian Rhythm of Blood Pressure in Patients with Hypertension". The authors are to be commended for identifying an independent association between an elevated uric acid/albumin ratio (UAR) and a non-dipper blood pressure pattern—an abnormal circadian rhythm known to predict adverse cardiovascular outcomes.

The study enriches the existing literature by suggesting a simple and low-cost biomarker for identifying high-risk hypertensive patients. However, while the retrospective design and lack of longitudinal data were acknowledged as limitations, we believe an additional aspect deserves further discussion: the potential of UAR as a therapeutic guide in hypertension management.

Recent evidence suggests that UAR is not only a surrogate of oxidative stress and systemic inflammation, but also a strong predictor of both cardiovascular and all-cause mortality. In a large prospective cohort study, Liu et al.[2] demonstrated that higher UAR levels were independently associated with increased risk of death, even after adjusting for traditional risk factors. Yin et al.[3] showed that elevated UAR levels may be an independent and effective biomarker for predicting poorly developed coronary collateral circulation development in Non-ST Elevation Myocardial Infarction patients.

Given these findings, several questions naturally arise:

- Could serial UAR measurements be used to track therapeutic response in hypertensive patients?
- Should a high UAR prompt more aggressive antihypertensive treatment, particularly in non-dipper profiles?
- Might urate-lowering or anti-inflammatory therapies offer additional benefit in patients with elevated UAR?
- Can UAR be incorporated into chronotherapeutic models, where treatment timing is individualized based on circadian risk patterns?[4]

As hypertension management evolves toward precision medicine, the need for accessible, dynamic and pathophysiologically relevant biomarkers becomes paramount. UAR may fulfill these criteria, but this promise requires validation in prospective, interventional studies. Particularly, studies examining whether targeted reduction in UAR leads to measurable improvements in cardiovascular outcomes would be of high clinical relevance.

We commend the authors for drawing attention to UAR as a novel biomarker in hypertension and encourage future research focused not only on its diagnostic relevance, but also on its potential to influence therapeutic decision-making.

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Reply to the Letter to the Editor: "Uric Acid/Albumin Ratio: Beyond Risk Stratification to Therapeutic Guidance in Hypertension"

Editöre Mektuba Yanıt: "Ürik Asit/Albümin Oranı: Hipertansiyonda Risk Stratifikasyonunun Ötesinde Terapötik Rehberlik"

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

To the Editor,

We thank the authors[1] for their interest and comments regarding our study, which demonstrated the relationship between the serum uric acid/albumin ratio (UAR) and the circadian rhythm of blood pressure (BP).[2]

In their initial comments, the authors brought attention to the potential role of serial UAR measurements as a complementary tool in assessing therapeutic response in patients with hypertension. Recent studies have demonstrated associations between UAR and established cardiovascular risk markers such as carotid intima-media thickness and peripheral artery disease severity in hypertensive patients.[3,4] However, both our study and the existing literature are predominantly cross-sectional in design. As such, there is a lack of longitudinal data demonstrating the dynamics of UAR in response to pharmacological or lifestyle interventions. Until such longitudinal evidence is available, we propose that UAR be regarded as a complementary biomarker rather than a definitive tool for assessing therapeutic response in hypertensive patients.

In their second comment, the authors raised an important question regarding whether a high UAR should prompt more aggressive antihypertensive treatment, particularly in patients with a non-dipper blood pressure profile. Non-dipper hypertensive patients are known to have a higher risk of cardiovascular events and target organ damage.[5] An elevated UAR reflects increased oxidative stress and inflammation, both of which contribute to vascular dysfunction and hypertension severity.[6] In this context, a high UAR may help identify patients at elevated risk—particularly those with a non-dipping profile—who might benefit from closer follow-up or adjunctive therapies aimed at reducing oxidative stress and inflammation. However, current evidence does not support intensifying antihypertensive treatment based solely on UAR values. At this stage, UAR should be considered a complementary marker in risk stratification, while treatment decisions should be based on comprehensive clinical assessment, including ambulatory blood pressure monitoring and assessment of end-organ damage.

In their third comment, the authors posed a thought-provoking question regarding whether patients with elevated UAR might derive additional clinical benefit from urate-lowering or anti-inflammatory therapies, particularly in the context of cardiovascular risk modulation. Current evidence indicates that UAR is not only associated with hypertension but also correlates with markers of atherosclerotic burden, endothelial dysfunction, and systemic inflammation.[2-4] Urate-lowering therapies, such as allopurinol and febuxostat, have been shown to reduce inflammation and improve endothelial function, potentially mitigating cardiovascular risk.[7] Similarly, anti-inflammatory agents like colchicine have demonstrated secondary cardiovascular protective effects in recent studies.[8] However, specific prospective data assessing the efficacy of these therapies in patient subgroups characterized by elevated UAR remain limited. Therefore, while these therapies may offer promise, robust prospective clinical trials are needed to determine their true benefit in patients with elevated UAR.

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We appreciate the authors' insightful question regarding the integration of UAR into chronotherapeutic models for hypertension management. Chronotherapy—administering antihypertensive medications at specific times to align with the body's circadian rhythms—has shown promise in improving BP control and reducing organ damage.[9] For instance, evening dosing of angiotensin receptor blockers like valsartan has been associated with better nocturnal BP control and a more pronounced nocturnal BP dip. Incorporating UAR into chronotherapeutic models could offer a personalized approach to hypertension treatment. By identifying patients with elevated UAR and non-dipping BP patterns, clinicians might tailor medication timing to optimize therapeutic outcomes. However, prospective studies are needed to validate this approach and establish UAR as a reliable biomarker for guiding chronotherapy in hypertensive patients.

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