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ABOUT JOURNAL

Koşuyolu Heart Journal is a peer-reviewed, open access e-journal that has been published three times a year in April, August and December. This is the scientific journal of the Health Sciences University Kartal Koşuyolu High Specialization Training and Research Hospital, (namely in Turkish, Sağlık Bilimleri Üniversitesi, Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, İstanbul, Türkiye).

The aim of the Koşuyolu Heart Journal; is to present advances in the field of cardiology, cardiovascular surgery, congenital cardiac surgery and cardiovascular anesthesia to the readers. Koşuyolu Heart Journal publishes research articles, reviews, original case reports and images, letters and critiques on cardiovascular medicine. The target reader population are the doctors specialized to the cardiovascular medicine. As an open access journal, all content is freely available.

Koşuyolu Heart Journal currently has an acceptance rate of 58%. The average time between submission and final decision is 40 days and the average time between acceptance and final printed publication is 13 weeks. However, provisional copy of submissions are published online within 1 month after acceptance.

Journal History :

- Koşuyolu Heart Journal, ISSN 1300-8706, 1990 - 2007.
- Koşuyolu Kalp Dergisi, ISSN 1300-8706, 2009 - 2014.
- Koşuyolu Heart Journal, ISSN 2149-2972, eISSN 2149-2980, 2015-2021.
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Submission Process: The manuscripts should be submitted via online.The journal do not charge any article submission or processing charges.

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EDITORIAL POLICIES

Aims and Scope

Koşuyolu Heart Journal aims to present advances in the field of cardiology, cardiovascular surgery, congenital heart surgery, and cardiovascular anesthesia to the readers. In order to achieve this goal, Koşuyolu Heart Journal publishes research articles (for the clinical or laboratory studies), reviews (by invitation only), case reports, original images, original techniques for cardiovascular surgery or cardiovascular interventions and letters/critiques on cardiovascular medicine. Koşuyolu Heart Journal publishes, after double blinded peer review, the articles for the target reader population consisting of cardiologists, cardiovascular surgeons and cardiac anesthesiologists. The articles should be submitted in English, while the title and abstract should be written in both English and Turkish. Editorial and publication process of Koşuyolu Heart Journal are congruent with the standards of ICMJE, WAME, and COPE. Koşuyolu Heart Journal is an open access journal.

Originality of Manuscript

The corresponding author must certify that their article is original, has not been published previously, and is not under consideration for publication by another journal. The corresponding author should affirm originality of the work in the Article Submission Form. If the work has been presented previously at a meeting as an oral or poster presentation, corresponding author must state the name, date and place of the meeting at the Title Page.

Autorship

An individual who has made substantial intellectual contributions to the article should be an author. Each author must have a role in all of the following areas:

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2. Writing article or revising it substantially.
3. Final approval of the submitted version.

Other contributors who perform technical support, identify patients for study, translate the texts, supply materials, provide funding have not been qualified as author. These contributions may be acknowledged in the manuscript. Author roles are stated at Article Submission Form.

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The Koşuyolu Heart Journal accepts the Declaration of Helsinki Principles as the policy of the Journal. Therefore, all studies concerning human subjects must be approved by the Institutional Review Board. All study subjects should be informed and written consent should be obtained. The editor may ask for a copy of the approval document.

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INSTRUCTIONS for AUTHORS

Scope of the Journal

The Koşuyolu Heart Journal is published three times a year (april, august, and december). The journal accepts articles in English language. However, the articles have the titles and abstracts written in English and Turkish language. Terms written in another language should be indicated within quotation marks in articles.

All manuscripts submitted for publication should comply with Uniform Requirements for Manuscripts Submitted to Biomedical Journals produced and updated by the International Committee of Medical Journals Editors (http://www.icmje.org/).

The Koşuyolu Heart Journal accepts the Declaration of Helsinki Principles (http:// www.wma.net/en/30publications/10policies/b3/index.html) as the policy of the Journal. Therefore, all manuscripts concerning human subjects must contain a statement in the Materials and Methods section, indicating that the study was approved by the Institutional Review Board. All study subjects should be informed and written consent should be obtained and this should be declared in the Materials and Methods section. All manuscripts dealing with animal subjects must contain a statement indicating that the study was performed according to The Guide for the Care and Use of Laboratory Animals (https://www.nap.edu/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals) with the approval of the Institutional Review Board, in the Materials and Methods section. The Editor may ask for a copy of the approval document. The journals editorial and publication process are also congruent with COPE (https://publicationethics.org/guidance/Guidelines) standards.

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Symbols, Units, and Abbreviations: In general, the Journal follows the conventions of Scientific Style and Format, The CSE Manual for Authors, Editors, and Publishers, Council of Science Editors, Reston, VA, USA (7th ed.). Please use SI units. Abbreviations should be internationally accepted and should be defined accordingly in the text in parenthesis when first mentioned and used in the text. The abbreviated form should be used all throughout the article.

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Keywords: There should be two to five key words complying with the Index Medicus Medical Subject Headings (MeSH) and Türkiye Bilim Terimleri for Turkish. Refer to https://meshb.nlm.nih.gov/search and https://www.bilimterimleri.com for English and Turkish key words, respectively.

Original Investigations are clinical or experimental research articles. They should include; Turkish title, Turkish structured abstract (limited to 300 words structured as Giriş, Hastalar ve Yöntem, Bulgular and Sonuç), Turkish key words and English title, English structured abstract (limited to 300 words structured as Introduction, Materials (or Patients) and Methods, Results and Conclusion), English key words. The other sections of the manuscript should include Introduction, Materials (or Patients) and Methods, Results, Discussion, Acknowledgement (if required) and References. All sections of the manuscripts should start on a new page. Research articles are not referred to exceed 5000 words and 40 references.

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Case Reports should include Turkish title, Turkish abstract, Turkish key words, English title, English abstract, English key words, Introduction, Case presentation, Discussion and References. Introduction and Discussion sections of the Case reports should be short and concise and the abstract should be prepared as one paragraph. Structured abstract is not required. Case reports should not exceed 1500 words and the number of references should not exceed 20.

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Tables and Figures: Tables, figures, graphics and pictures should be numbered with Arabic numbers in order of reference in the text. Localization of tables, figures, graphics and pictures should be indicated.

Each table should be prepared with double spacing on a separate page. Tables should have a brief title. Authors should place explanatory matter in footnotes not in the heading. Explanations should be made for all nonstandard abbreviations in footnotes. The following symbols should be used for abbreviations in sequence: *,

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Figures should be either professionally drawn or photographed, and these items should be submitted as photographic-quality digital images. Figures should be submitted in a format that will produce high-quality image (for example, JPEG or GIF). Authors should control the images of such files on a computer screen before submitting them to be sure they meet their own quality standards. Information on staining and microscopic images, the magnification ratio.

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Example: Suárez De Lezo J, Medina A, Pan M, Romero M, Segura J, Pavlovic D, et al. Transcatheter occlusion of complex atrial septal defects. Catheter Cardiovasc Interv 2000;51:33-41.

If the reference is a journal supplement;

Author(s)' surname and initial(s) of the first name. Title of the article. Title of the manuscript abbreviated according to Index Medicus (http://www.ncbi.nlm.nih. gov/sites/entrez/query.fcgi?db=nlmcatalog). Year;Volume(Suppl Supplement number):First and last page number.

Example: Parsonnet V, Lean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989;79(Suppl 1):S3-S12.

If the reference is a book;

Author(s)' surname and initial(s) of the first name. Title of the book. Edition number. City of publication, Country: Publisher, Year of Publication: Page numbers.

Example: Borrow K, Braunwald E. Heart Disease. 1st ed. Philadelphia, PA, USA: WB Saunders, 1988:976.

If the reference is a book chapter;

Surname and initial(s) of the first name of the author(s) of the chapter.Title of the chapter. In: Surname and initial(s) of the first name(s) of the editor(s) (ed) or (eds). Title of the book. Edition number. City of publication, Country: Publisher,

Year of publication: First and last page numbers of the chapter.

Example: Nguyen A, Imoto E, Eklof BGH. Pulmonary embolism. In: Barros DSa AAB, Chant ADB (eds). Emergency Vascular and Endovascular Surgical Practice. 2nd ed. London, UK: Hodder Arnold, 2005:251-60.

If the reference is an article presented in a meeting;

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Publisher; Year. Page numbers.

Example: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O (eds). MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. North-Holland; 1992. p. 1561-5.

If the reference is an online journal;

Author(s)' surname and initial(s) of the first name (all authors if the number of authors are 6 or less, first 6 authors if the number of authors of an article is more than 6 followed by "et al." in international references). Title of the article, title of the manuscript abbreviated according to Index Medicus Year; Volume (Number). Available from: URL address. Accessed date:day. month.year.

Example: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis 1995;1(1). Available from: http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed date: 25.12.1999.

If the reference is a website;

Name of the web site. Access date. Available from: address of the web site.

Example: World Health Organization (WHO). Access date: 9 July 2008. Available from: http://www.who.int

If the reference is a thesis;

Author's surname and initial of the first name. Title of the thesis (Thesis). Name of the university (or educational hospital, institution, etc), City, Country, Year.

Example: Kalender M. The effect of using internal mammarian artery graft on coronary bypass morbidity and mortality in octogenarian. (Thesis). Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, İstanbul, Türkiye, 2011.

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Evaluation of Cardiovascular Autonomic Dysfunction According to Heart Rate Turbulence and Variability in Patients with Benign Paroxysmal Positional Vertigo

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ABSTRACT

Introduction: The relationship between benign paroxysmal positional vertigo (BPPV) and cardiovascular autonomic dysfunction is not clear. Disruption of the balance between the sympathetic and parasympathetic systems causes various diseases. It is believed that disorders of the parasympathetic system, particularly, may be responsible for causing BPPV. Heart rate variability (HRV) and HRT (heart rate turbulence), which show autonomic dysfunction, are two non-invasive tests that show the relationship of the heart rate with the autonomic nervous system. The purpose of the present study was to evaluate the relationship between autonomic dysfunction and BPPV in patients with BPPV by using HRV and HRT, which are non-invasive laboratory parameters.

Patients and Methods: A total of 100 age- and gender-matched volunteers and 100 patients with BPPV were selected for the study between January 2015 and January 2020. We obtained HRT and HRV parameters from 24-hour ECG Holter recordings. We considered a TO above 0 and a TS above 2.5 to be abnormal. We compared the parameters between groups.

Results: A significant difference was observed between the BPPV and control groups in the HRV parameters SDNNI (p= 0.036), SDANN (p= 0.045), and HRT parameter TS (p= 0.048). We showed that abnormal TO (p= 0.025) and TS (p= 0.038) values were significantly higher in the patient group.

Conclusion: Parasympathetic autonomic dysfunction was demonstrated by the lower HRV and HRT values observed in the patients with BPPV compared to the control group in the present study. The present findings must be confirmed with a much larger number of patients and multi-center studies.

Key Words: Benign paroxysmal positional vertigo; autonomic nervous system disorders; dizziness

Benin Paroksismal Pozisyonel Vertigolu Hastalarda Kardiyovasküler Otonomik Disfonksiyonun Kalp Hızı Türbülansı ve Değişkenliğine Göre Değerlendirilmesi

ÖZET

Giriş: *Benign Paroxysmal Positional Vertigo* (BPPV) ile otonomik disfonksiyonun ilişkisi net değildir. Sempatik ve parasempatik sistem arasındaki dengenin bozulması çeşitli hastalıklara sebep olmaktadır. Özellikle parasempatik sistem bozukluklarının BPPV'ye sebep olabileceği düşünülmektedir. Otonomik disfonksiyonu gösteren HRV (*heart rate variability*) ve HRT (*heart rate turbulence*) kalbin kalp hızının otonomik sinir sistemi ile ilişkisini gösteren iki non-invaziv testtir. Bu çalışmadaki amacımız BPPV'li hastalarda otonomik disfonksiyon ile BPPV arasındaki ilişkiyi non-invaziv bir laboratuvar parametresi olan HRV ve HRT parametrelerini kullanarak değerlendirmektir.

Hastalar ve Yöntem: Çalışma için Ocak 2015-Ocak 2020 tarihleri arasında yaş ve cinsiyet uyumlu 100 gönüllü, 100 BPPV hastası seçilmiştir. Hastaların 24 saatlik EKG holter kayıtları analiz edilmiştir. Bu kayıtlardan HRT ve HRV parametreleri elde edilmiştir. Parametreler gruplar arasında kıyaslanmıştır. TO 0´ın ve TS 2.5'in üzeri anormal kabul edilmiştir. Gruplardaki anormal TS ve TO değerleri kıyaslanmıştır.

Bulgular: HRV parametrelerinden SDNNI (p= 0.036) SDANN (p= 0.045) ve HRT parametrelerinde TS (p= 0.048) arasında BPPV ve kontrol grubu arasında anlamlı derecede farklılık izlendi. Anormal TO (p= 0.025) ve TS (p= 0.038) değerleri hasta grupta anlamlı düzeyde daha fazla izlendi.

Sonuç: Bu çalışmada BPPV'li hastaların kontrol grubuna göre HRV ve HRT değerlerinin düşük olması, parasempatik otonomik disfonksiyonu olduğunu düşündürmektedir. Mevcut bulguların çok daha fazla hasta sayısı ve çok merkezli çalışmalarla doğrulanması gerekmektedir.

Anahtar Kelimeler: Benin paroksismal pozisyonel vertigo; otonomik sinir sistemi bozuklukları; baş dönmesi

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INTRODUCTION

Vertigo is perceived as an imaginary illusion of movement. Positional vertigo is defined as the sensation of rotation caused by gravity with the relative change in head position. The most common cause of positional vertigo is benign paroxysmal positional vertigo (BPPV), which is defined as an inner ear disorder characterized by recurrent episodes of positional vertigo. It is known to affect approximately 5.6 million people (17-42%) annually in the US[1]. Twenty percent of BPPV patients can recover spontaneously in one month and 50% in three months. Although BPPV affects all three canals, posterior canal BPPV (85-95%) is the most common. The second most common is lateral/horizontal canal BPPV (5-15%), and superior/anterior canal BPPV is very rare (1%). Physiopathologically, the displacement of otoconia in the canal (canalothiasis) is the most common cause and results in nystagmus and vertigo. Horizontal-rotatory nystagmus observed during the Dix-Hallpike Test is particularly diagnostic for posterior BPPV. Canalith Reposition Maneuver (Epley) and Semont Maneuver are used in the treatment. In the diagnosis of lateral canal BPPV, horizontal nystagmus in the Supine Head Roll Test (Pagnini-Lempert or Pagnini-McClure Roll Test) is diagnostic. Gufoni Maneuver can be used in treatment. Most patients are relieved with these maneuvers and require less medical treatment[2].

The autonomic nervous system operates in a state of delicate balance between sympathetic and parasympathetic innervation. The relations of the vestibular system with the autonomic system have been the subject of curiosity of researchers to date. It is known that patients and animals that have vestibular dysfunctions also have clinical presentations of autonomic dysfunction and patients with autonomic dysfunction present with symptoms such as dizziness and tinnitus. The mechanism by which the vestibular system and the autonomic system are affected and the cause-effect relationships are not clearly known yet[3]. The Head Up Tilt Test, which evaluates orthostatic hypotension and autonomic dysfunction, and beat-to-beat systolic pressure measurements were used to investigate this relation[4]. However, the measurement of heart rate variability (HRV) and heart rate turbulence (HRT) parameters using a 24-hour Holter monitor, which has not been previously studied, is considered the most common noninvasive testing method for evaluating the sympathetic and parasympathetic systems. Heart rate turbulence refers to the physiological short-term baroreflex-regulated fluctuations in the sinus rhythm following premature ventricular contraction (PVC). Turbulence onset (TO) values, which indicate the initial increase in heart rate following a ventricular premature beat, and turbulence slope (TS) values, which reflect the subsequent heart rate slowing, are utilized to evaluate heart rate turbulence (HRT)[5].

Heart rate variability is also very important in the evaluation of autonomic dysfunction like HRT, which is called cyclic fluctuations in heart function between successive heartbeats (i.e. RR intervals) and at rest. The retraction of vagal tone and increased sympathetic activity, leading to decreased HRV, is believed to be associated with the development of life-threatening arrhythmias[6].

The purpose of the present study was to evaluate the relationship between autonomic dysfunction and BPPV in patients with BPPV using non-invasive laboratory parameters such as HRV and HRT.

PATIENTS and METHODS

Study Design and Patient Selection

A total of 100 age- and gender-matched volunteers and 100 BPPV patients were selected for the study between January 2015 and January 2020. The 100 volunteers consisted of patients who applied to the otolaryngology outpatient clinic for any reason, and BPPV patients were patients who applied to the otolaryngology clinic with dizziness and were then diagnosed with idiopathic BPPV by various maneuver tests (e.g. Dix-Hallpike, Supine Roll). Permission was obtained from the local ethics committee for the study, and informed consent was obtained from the patients. The study was approved by the local Ethics Committee (30.04.2021-2021/06). The study was conducted in accordance with the guidelines of the Declaration of Helsinki, the principles of Good Clinical Practice, and with due respect for the rights and dignity of all participants involved. Verbal informed consent was obtained from participants following a brief explanation of the aim of the study.

Inclusion and Exclusion Criteria

The diagnosis of BPPV was established based on a history of new-onset vertigo that occurred during specific positional changes and was confirmed through maneuver tests. All patients with BPPV were treated with the Canalith Reposition Maneuver for the affected canal.

The exclusion criteria were vestibular neuritis or head injury, use of drugs affecting the autonomic system (e.g. anticholinergics, antiarrhythmics, sympathomimetics, parasympathomimetics), those with neurological and metabolic diseases, hypertension and diabetes, patients with chronic vertigo and any heart disease (e.g. atrial fibrillation, other rhythm disorders, myocardial infarction).

Serum electrolyte values, atrial conduction times measured on ECG, and echocardiography parameters were normal in all patients and the control group.

Measurements

The 24-h Holter ECG (Reynolds Medical Pathfinder Software Version V8.255; Reynolds Medical, Hertford, UK) monitoring was performed for all patients. Holter ECG monitoring was conducted on the day of BPPV diagnosis for the patient group. Holter records were kept by excluding the artifacts. Since the HRT data could not be obtained in patients without PVC, such patients were excluded from the study.

The HRT parameters (TO and TS) were calculated by using a computer software (HRT View Software Version 0.60-0.1, Munich, Germany), and TO was expressed as the percentile difference between the 2 RR intervals that were measured just after a VPB and just before a VPB. The TS value was defined and calculated as the maximum positive slope of a regression curve obtained from any set of five consecutive RR intervals in the first 20 sinus rhythm intervals after a VPB. The TO value was calculated separately for each VPB and the final data were defined as the mean values of these individual measurements. An abnormal TO value was defined as ≥0%, while an abnormal TS value was defined as ≤2.5 ms/RR[7].

The HRV analysis was made in all participants according to the Guidelines of the European Society of Cardiology and the North American Society of Pacemakers and Electrophysiology, and HRV measurements were made from 24-hour Holter ECG recordings[8]. The evaluation of HRV was performed by using a computer program (Cardioscan 12.0, DMS, Ventura, CA, the USA). The 6-hour part at night was determined following the marked day-night shift in the length of RR intervals.

The HRV measurements included the standard deviation of all normal sinus RR intervals over 24 hours (SDNN), the mean value of all normal sinus RR intervals (SDNNI) for all 5-minute segments, the standard deviation of the mean normal sinus RR intervals for all 5-minute segments (SDANN), the root-mean-square difference of the sequential normal sinus RR interval (rMSSD), and the percentage of the consecutive normal sinus RR intervals >50 ms (sNN50).

Statistical Analysis

All analyses were made by using the SPSS software version 24 (IBM Corp., Armonk, NY, the USA). A p-value of <0.05 was considered significant. Distributions of HRT and HRV parameters in MS and control groups were analyzed by using the Shapiro-Wilk Test. Continuous data that did not have a normal distribution were compared with the Mann-Whitney U-Test. Categorical parameters were evaluated and compared with the Chi-square Test. The HRT and HRV values were adjusted for age with the Covariance Analysis. For descriptive statistics, frequencies were used in categorical data, and median and interquartile ranges were used for non-normally distributed quantitative data. Correlation analyses were performed by using Spearman's Rank Correlation Coefficients. Additionally, a post-hoc power analysis was performed to confirm that the current study had sufficient power (99%).

RESULTS

Among the 100 BPPV patients, 66 were female and 34 were male, and the mean age was 41.6 ± 10.2. Among the 100 control patients, 64 were female and 36 were male, and the mean age was 40.8 ± 9.8 years (Table 1).

There were no differences in the mean heart rates between the groups. SDNN, rMSSD, sNN50, and TI results of HRV parameters were statistically similar between the two groups. Also, HRV parameters such as SDNNi, and SDANN were significantly different in the BPPV group when compared to the control group (50.18 ± 21.92; 54.23 ± 20.26 p= 0.036; 116.12 ± 46 ± 94; 122.91 ± 39.18 p= 0.045 respectively). There was no significant difference between the two groups in TO, one of the HRT parameters. Significant differences were detected in TS one of the HRT parameters between the groups (35.19 ± 25.15; 13.15 ± 9.11 p= 0.048, respectively) (Table 2).

A TO value of ≥0% and an S value of ≤2.5 ms/RR were considered abnormal. Significant differences were observed between the two groups in terms of abnormal TO and TS parameters (68%; 19% p= 0.025, 64%; 21% p= 0.038) (Table 3).

Table 1. Demographic characteristics of the patients with BPPV and controls

	Patients with BPPV (n= 100)	Controls (n= 100)	p
Age (years) (mean±SD)	41.6 ± 10.2	40.8 ± 9.8	0.435
Sex (number of females)	66/100 (66%)	64/100 (64%)	0.387

SD: Standard deviation.

Table 2. HRT and HRV parameters of the patients with BPPV vs controls

		Patients with BPPV	Controls	p
HRT	TO	-0.04 ± 0.03	-0.08 ± 0.36	0.124
	TS	35.19 ± 25.15	13.15 ± 9.11	0.048
HRV	SDNN	128.98 ± 47.92	135.95 ± 42.14	0.224
	SDNNI	50.18 ± 21.92	54.23 ± 20.26	0.036
	SDANN	116.12 ± 46 ± 94	122.91 ± 39.18	0.045
	rMSSD	35.51 ± 30.60	35.09 ± 19.50	0.214
	sNN50	10853.05 ± 1267.53	9835.14 ± 8869.78	0.156
	TI	34.84 ± 12.42	34.12 ± 6.5	1

HRT: Heart rate turbulence, HRV: Heart rate variability, BPPV: Benign paroxysmal positional vertigo, TI: Triangular index, TO: Turbulence onset; TS: Turbulence slope, SDNN: Standard deviation of NN intervals, SDNNI: SDNN index, SDANN: Standard deviation of the average NN intervals for each 5-min segment, rMSSD: Root-mean-square of successive RR interval differences, sNN50: Percentage of successive RR intervals that differ by more than 50 ms.
*p< 0.05

Table 3. Abnormal HRT parameters of the patients with BPPV and controls

	Patients with BPPV	Controls	p
Abnormal TO	68/100 (68%)	19/100 (19%)	0.025*
Abnormal TS	64/100 (64%)	21/31 (21%)	0.038*

SD: Standard deviation, HRT: Heart rate turbulence, BPPV: Benign paroxysmal vertigo, TO: Turbulence onset, TI: Triangular index.

DISCUSSION

Despite previous studies demonstrating various causes of vertigo's pathophysiology, the mechanisms of the vestibular system are still not fully understood. Vertigo associated with autonomic dysfunction (AD), orthostatic hypotension (OH), or mitral valve prolapse (MVP) may be the cause of dizziness experienced by an individual who has an autonomic disorder. Since the pathophysiology of such diseases is complex, their treatment becomes more difficult. These patients are often misdiagnosed with conditions such as hypoglycemia, chronic fatigue syndrome, neurocardiogenic syncope, or psychiatric disorders[3]. Vertigo that is associated with autonomic dysfunction has been reported in many previous studies, which showed that dysautonomia on postural changes may play important roles in the development of vertigo, and is provoked by disturbances of the autoregulatory mechanisms of cerebral blood flow[9]. Many non-invasive tests (e.g. Hyperventilation Test, Tilt Test) were used in the past for vertigo and dizziness to monitor autonomic dysfunction[10].

The semicircular canals are responsible for sensing the angular head movement in three-dimensional space providing input from the central nervous system (CNS) required for rapid mobility, stable vision, and autonomic control of cardiovascular and other gravity-sensitive systems. Disturbances altering the canal mechanics result in pathological inputs to the CNS often leading to attenuating symptoms[11]. The most important pathology in BPPV is the mechanical stimulation of vestibular receptors by displaced otoconia in the Semicircular Canals (SCCs) without a true rotation of the head[12]. It was shown that the vestibular system participates in autonomic regulation that regulates cardiovascular control during body movement and postural changes[13].

One-third of patients who have BPPV have some abnormality in the autonomic system response, as indicated by orthostatic hypotension with the Tilt Test or by the blood pressure response during the Valsalva Maneuver. The rate of autonomic dysfunction is higher in patients with residual vertigo than in those without[14]. Despite the occasional success of repositioning treatments in BPPV patients, the underlying pathophysiological mechanisms remain largely unknown. Notably, the mechanism of autonomic dysfunction has not been investigated in relation to BPPV thus far.

The HRV parameter is used to evaluate the tonic vagal activity[15]. Vagal tone is dominant during rest, but vagal and sympathetic activities are in a constant balance. Decreased HRV is detected in patients with multiple sclerosis, heart failure, diabetic neuropathy, or myocardial infarction[8,14,15]. It was shown in the study of Kim HA et al. that the residual dizziness after successful treatment in BPPV may be partly related to sympathetic neural autonomic dysfunction[14].

It was observed in our study that HRV parameters such as SDNNi, and SDANN were decreased significantly in BPPV patients when compared to the control group.

The deterioration in HRT parameters indicates cardiac autonomic dysfunction associated with decreased baroreflex sensitivity and decreased parasympathetic activity. In many previous studies, abnormal HRT parameters were reported in various diseases, and the findings were associated with an impaired baroreflex response[17,18]. In the present study, significant differences were detected between the TS one of the HRT parameters between BPPV and the control group. Based on these findings, it can be suggested that there is a decrease in baroreflex sensitivity and parasympathetic activity in individuals with BPPV.

The decreased HRV and HRT parameters observed in BPPV patients indicated a decrease in autonomic functions, specifically a decrease in the parasympathetic system, along with an increase in sympathetic activity.

The main limitation of our study was the absence of Spectral HRV Analysis, which resulted in the measurement of only parasympathetic tone while the measurement of overall parasympathetic tone could not be conducted. Another limitation of the study was the lack of a gold standard diagnostic test for evaluating autonomic dysfunction. However, similar methods were employed in all studies in the literature.

CONCLUSION

Benign paroxysmal positional vertigo is the most common known cause of peripheral vertigo. Although two main pathophysiological mechanisms such as cupulolitiasis and canalolithiasis were emphasized in this regard, its pathophysiology has not yet been fully elucidated. In conclusion, in the present study, the lower HRV and HRT values of patients who have BPPV when compared to the control group showed parasympathetic autonomic dysfunction. The current findings need to be validated through larger sample sizes and multi-center studies to ensure their robustness and generalizability.

Ethics Committee Approval: The study was approved by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (Decision no: 2021/6, Date: 30.04.2021).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - İED; Analysis/Interpretation - SK; Data Collection - ÇG; Writing - İED, EY; Critical Revision - SK; Final Approval - İED; Statistical Analysis -İED; Overall Responsibility - İED.

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

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The Relationship Between Atherosclerotic Risk Factors and Female Gender

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ABSTRACT

Introduction: Identification and control of cardiovascular risk factors form the basis of strategies for protecting cardiovascular health. However, according to the results of many studies, women are less aware of their own risk factors and participate less in screening programs than men. This study was conducted to determine the risk of experiencing atherosclerotic events and risk-related factors in women aged 40-79 years.

Patients and Methods: This retrospective, cross-sectional analysis was conducted by the primary physician of the laboratory values used in atherosclerotic cardiovascular disease (ASCVD) risk assessment, who applied to the consultant outpatient clinics (pulmonary diseases, infectious diseases, nephrology, internal medicine outpatient clinics) in a training and research hospital between September and November 2021. The data of 131 female patients between the ages of 40-79 were analyzed.

Results: The average age of the 131 women included in the study was 51.6 years. It was observed that women predominantly had three or four risk factors. The five most common risk factors identified were as follows: a total cholesterol level above 170 mg/dL (86.3%), menopause (65.6%), HDL cholesterol below 50 mg/dL (64.1%), systolic blood pressure above 130 mmHg (56.4%), and smoking (32.1%). In the study, when investigating the relationship between the ASVCD risk calculator, atherosclerosis risk factors, and the menopausal period, statistically significant associations were observed between age, systolic blood pressure, total cholesterol, HDL, LDL, 10-year risk ratio, optimal risk ratio, and lifetime risk ratio.

Conclusion: The study determined that the average lifelong expected ASCVD risk among the women participating in the study, in terms of cardiovascular diseases, was 39.87 ± 8.81%. This finding highlights the significance of cardiovascular diseases and underscores the importance of conducting comprehensive risk assessments at the individual level to prevent them.

Key Words: Atherosclerosis; cardiovascular diseases; menopause; risk assessment; women's health

Aterosklerotik Risk Faktörleri ile Kadın Cinsiyeti Arasındaki İlişki

ÖZET

Giriş: Kardiyovasküler risk faktörlerinin tanımlanması ve kontrolü kalp sağlığını koruyucu stratejilerin temelini oluşturmaktadır. Ancak yapılan birçok çalışma sonucuna göre kadınlar erkeklere göre kendi risk faktörlerini daha az fark etmekte ve tarama programlarına daha az katılmaktalardır. Bu çalışmanın amacı 40-79 yaş arası kadınlarda aterosklerotik olay yaşama riskini ve riskle ilişkili faktörleri saptamaktır.

Hastalar ve Yöntem: Bu retrospektif, kesitsel analiz ile bir eğitim araştırma hastanesindeki kardiyoloji poliklinikleri dışında hizmet veren konsültan polikiniklerine (göğüs hastalıkları, enfeksiyon hastalıkları, nefroloji, dahiliye polikliniklerine) Eylül-Kasım 2021 tarihleri arasında başvuran, aile öyküsü olan, ASCVD risk değerlendirmesinde kullanılan laboratuvar değerlerinin primer hekimi tarafından çalıştırılmış ve 40-79 yaş arasındaki 131 kadın hastanın verileri incelenmiştir.

Bulgular: Çalışmaya dahil edilen 131 kadının yaş ortalaması 51.6 olarak bulundu. Kadınların çoğunlukla üç veya dört risk faktörü taşıdığı görüldü. En sık görülen ilk beş risk faktörü sırasıyla; total kolesterol düzeyinin 170 mg/dL üstü olması (%86.3), menopoz (%65.6), HDL kolesterolun 50 mg/dL altı olması (%64.1), sistolik kan basıncının 130 mmHg üstü olması (%56.4) ve sigara kullanımı (%32.1) olarak saptandı. Çalışmada ASVCD risk hesaplayıcısı ateroskleroz risk faktörleri ile menopozal dönem arasındaki ilişki incelendiğinde; yaş, sistolik kan basıncı, total kolestrol, HDL, LDL, 10 yıllık, optimal ve lifetime risk oranları arasında istatistiksel olarak anlamlılık saptandı ($p< 0.05$).

Sonuç: Çalışmaya katılan kadınların kardiyovasküler hastalıklar açısından yaşam boyu beklenen ASCVD risk ortalamasının %39.87 ± 8.81 olduğu saptanmıştır. Bu bulgu kardiyovasküler hastalıkların ne derece önemli bir sağlık sorunu olduğunu ve önlenmesi amacıyla bireysel düzeyde kapsamlı bir risk değerlendirmesinin yapılması gerekliliğini ortaya koymaktadır.

Anahtar Kelimeler: Ateroskleroz; kardiyovasküler hastalıklar; menopoz; risk değerlendirmesi; kadın sağlığı

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INTRODUCTION

Achieving good health requires engaging in multidimensional and complex processes. Diseases stemming from atherosclerosis, such as cardiovascular diseases (CVD) and stroke, stand as the leading cause of morbidity and mortality worldwide, particularly in industrialized societies[1].

Atherosclerosis, characterized by thickening and hardening of the arterial walls, is the leading cause of heart attacks and strokes[1,2]. Identification and control of cardiovascular risk factors form the basis of strategies to protect heart health. However, according to the results of many studies and the European Society of Cardiology Red Alert in Women's Heart Report, women are less aware of their own risk factors and participate less in screening programs than men[3-6].

Worldwide, approximately 17 million people die annually from CVD-related causes[5]. According to the 2018 data provided by the Turkish Statistical Institute (TÜİK), circulatory system diseases, accounting for 38.4% of all reported deaths, remained in the top position as observed in previous years. Among the cases of circulatory system diseases contributing to the mortality rate, 39.7% are attributed to ischemic heart diseases, 22.4% to cerebrovascular diseases, and 8.3% to hypertensive diseases[7]. According to the 2017 data of the Heart Diseases and Risk Factors in Turkish Adults (TEKHARF) study, it is estimated that there are approximately 3.5 million coronary heart patients in our country, this number increases by 4% per year in our aging population, and 210 thousand individuals die from coronary heart disease annually[8]. When the data of TÜİK and TEKHARF studies are combined, deaths due to atherosclerosis seem to be responsible for almost half of all deaths[7-9].

It is known that CVD, which is one of the leading causes of mortality and morbidity, develops due to risk factors at a rate of at least 80% and that CVD-related morbidity and mortality can be significantly reduced by optimizing risk factors[10,11]. Evaluation of the risk posed by this process, which starts at an early age, is of significant importance in terms of prevention and treatment[12,13].

For this reason, various kinds of risk calculation methods have been developed based on the evaluation of atherosclerotic risk factors. Estimating the risk of developing cardiovascular disease in adults is particularly important in terms of both preventive approaches and treatment.

Atherosclerotic heart disease typically progresses gradually over the years, and by the time symptoms become apparent, the condition is often already at an advanced stage. The importance of calculating social risk and combating risk factors in reducing mortality and morbidity is clearly evident. In the assessment of cardiovascular risk, various existing scoring systems such as the Framingham Risk Score, Reynolds Risk Score, SCORE (Systematic Coronary Risk Evaluation) Study, Joint British Societies (JBS2) Guide, and ASCVD (Atherosclerotic Cardiovascular Disease) Risk Algorithm are commonly employed. However, one significant limitation of these scoring systems is that they primarily focus on determining the 10-year risk of cardiovascular disease (CVD). Yet, it is crucial to assess not only the risks within a 10-year timeframe but also the lifetime CVD risks, particularly in women[5,10].

While many CVD risk factors are shared between women and men, studies have identified gender differences, particularly in relation to diabetes and dyslipidemia. Additionally, it has been observed that women who experience pregnancy-induced hypertension, gestational diabetes, and polycystic ovary syndrome have a higher risk of developing CVD[13,14].

The objective of this study was to assess the risk of atherosclerotic events and associated risk factors among women aged 40-79 years. The rationale for focusing on women was their relatively lower awareness of personal risk factors and lower participation in screening programs compared to men. Atherosclerotic heart diseases were specifically chosen as they represent one of the leading causes of mortality.

PATIENTS and METHODS

Study Data, Participants, and Design

This study was designed as a retrospective, cross-sectional investigation with a focus on identifying the risk of atherosclerotic events and associated risk factors among women aged 40-79 years.

In this study, conducted in collaboration with a thoracic and cardiovascular surgery training and research hospital, the primary physician assessed the laboratory values used in the risk assessment of atherosclerotic cardiovascular disease (ASCVD). The study included patients who sought consultation at various specialist polyclinics such as chest diseases, infectious diseases, nephrology, and internal medicine outpatient clinics, excluding the cardiology outpatient clinics. The data collection period for the study was between September and November 2021. Data from 131 female patients between the ages of 40-79 were included. The age range of 40-79 encompasses an important stage in a woman's life, which includes the climacteric period and menopause, significant for heart health.

The exclusion criteria were the following:

- Individuals with serum LDL cholesterol levels above 190
- Pregnancy and lactation status
- Individuals with alcohol dependence, substance abuse

- Use of oral contraceptives, postmenopausal hormone therapy
- Individuals with a history of major surgery
- Individuals with acute or chronic infection
- Individuals with cerebrovascular accident, ischemic heart disease, peripheral artery disease, venous thrombosis, chronic venous failure, or heart failure symptoms/diagnosis.

Research Variables

Dependent Variables of the Study: Atherosclerotic risk factors

Independent Variables of the Study: Female gender

Data Collection Tools

Data Containing Personal Information: In accordance with the literature, the researchers utilized socio-demographic data, health status indicators (including the presence of chronic diseases such as diabetes and hypertension, blood pressure values, select blood test results, aspirin usage, etc.), and information pertaining to healthy lifestyle behaviors (specifically, smoking status) to calculate the ASCVD Risk Algorithm and associated parameters.

Risk Calculation and Atherosclerotic Risk Factors: The risk of experiencing an atherosclerotic event for each woman in the study group was assessed based on the 2013 ACC/AHA(ESC SCORE) Guideline on the Assessment of Cardiovascular Risk and the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. The risk score calculation is performed online using a specific risk calculator. This calculator is designed for individuals without a history of atherosclerotic cardiac disease and with LDL cholesterol levels below 190 mg/dL. In this calculation method, the individual's risk of experiencing an atherosclerotic event, which includes both fatal and non-fatal myocardial infarction and fatal or non-fatal ischemic stroke, is estimated for both the next 10 years and for their lifetime. According to the calculator, several factors were considered as risk factors for atherosclerotic events. These factors include being an active smoker, having a total cholesterol level above 170 mg/dL, having an HDL cholesterol level below 50 mg/dL, having a systolic blood pressure above 130 mmHg, being diabetic, and using an antihypertensive agent.

Blood Pressure: Blood pressure recordings were obtained by using a mechanical sphygmomanometer after a 15-minute period of rest.

Evaluation of Data

Descriptive analyses, including frequency and percentage calculations, were performed on the research data. To assess differences, Chi-square and Fisher's exact tests were used. In addition, logistic regression was employed to examine the relationship using Spearman's rho effect. The data analysis was conducted using PSPP (GNU pspp 0.10.4-g50f7b7) and Microsoft Excel software.

RESULTS

The average age of the 131 women included in the study was determined to be 51.6. The five most common risk factors identified in the study were as follows: total cholesterol level above 170 mg/dL (86.3%), menopause (65.6%), HDL cholesterol below 50 mg/dL (64.1%), systolic blood pressure above 130 mmHg (56.4%), and smoking (32.1%) (Table 1).

Figure 1 reveals that the majority of women in the study had three or four risk factors. Specifically, 31.3% (n= 41) of individuals had three risk factors, 37.4% (n= 49) had four risk factors, and 14.5% (n= 19) had five risk factors.

When analyzing the blood pressure and cholesterol levels of the participants, it was found that the mean systolic blood pressure was 135.52 ± 22.91, the mean HDL cholesterol level was 46.98 ± 10.68, and the mean LDL cholesterol level was 135.88 ± 32.48. It was observed that these values followed a normal distribution, as indicated in Table 2.

Table 1. Distribution of risk factors among the participants (n= 131)

	Yes		No		
Risk factors	**n**	**%**	**n**	**%**	**p**
Smoking	42	32.1%	89	67.9%	0.001
Total cholesterol level above 170 mg/dL	113	86.3%	18	13.7%	0.001
Systolic blood pressure greater than 130 mmHg	74	56.4%	57	43.5%	0.001
HDL cholesterol below 50 mg/dL	84	64.1%	47	35.9%	0.001
Being diabetic	30	22.9%	101	77.1%	0.001
Using an antihypertensive agent	32	24.4%	99	75.6%	0.001
Menopause	86	65.6%	45	34.4%	0.001

HDL: High density lipoprotein

Figure 1. The ratio of the individuals included in the study by the number of risk factors (n= 131).

While the 10-year atherosclerosis risk rate of the participants was 0%, the highest was 57.0% (n= 131). The mean 10-year risk of atherosclerotic event among the participants was 6.61 ± 8.31% (n= 131). The optimal risk ratios ranged from 0% to 19.0%, with an average of 1.37 ± 2.62%. On the other hand, the lifetime risk ratio varied from 8.0% to 50.0%, with an average of 39.87 ± 8.81% (n= 113), as presented in Table 3.

In the study, a significant relationship was observed between the ASVCD risk calculator, atherosclerosis risk factors, and the menopausal period. The variables that showed a statistically significant difference (p< 0.05) included age, systolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, 10-year risk ratio, optimal risk ratio, and lifetime risk ratio (Table 4). It was observed that the mean ASCVD calculation parameters were elevated during the menopausal period, except for HDL cholesterol.

Table 2. Blood pressure and cholesterol levels of the participants (n= 131)

Parameter	Avg ± SD	Normal range	Distribution type
Systolic blood pressure	135.52 ± 22.91	90-130	ND
HDL (mg/dL)	46.98 ± 10.68	35-70	NR
LDL (mg/dL)	135.88 ± 32.48	<150	NR
Total cholesterol (mg/dL)	216.98 ± 41.28	<200	ND

NR: Normal range, ND: Non-normal distribution, HDL: High density lipoprotein, LDL: Low density lipoptrotein.

Table 3. Expected 10-year risk ratio calculated in participants (n= 131)

Parameter	n	Min	Max	Avg ± SD
10-year risk of ASCVD %	131	0	57	6.61 ± 8.31
Optimal risk of ASCVD % (40-79 years)	131	0	19	1.37 ± 2.62
Lifetime risk of ASCVD % (40-59 years)	113	8	50	39.87 ± 8.81

SD: Standart deviation, ASCVD: Atherosclerotic cardiovascular disease

Table 4. Relationship between ASCVD calculator parameters and being in menopause (n= 131)

Risk Factors	Not in menopause	In menopause	p**
Age	43.20 ± 3.07	56.05 ± 7.12	0.00001*
Systolic blood pressunre	127.20 ± 14.96	139.87 ± 25.13	0.0004*
Dystolic blood pressure	76.71 ± 14.24	80.07 ± 15.16	0.2212
Total cholestrol	203.11 ± 36.46	224.23 ± 41.99	0.0050*
HDL	41.69 ± 8.59	49.76 ± 10.67	0.00001*
LDL	127.82 ± 29	140.09 ± 33.44	0.0391*
Expected in 10 years	3.13 ± 2.78	8.43 ± 9.58	0.00001*
Optimal	0.04 ± 0.21	2.06 ± 3.01	0.00001*
Lifetime	36.56 ± 11.62	42.06 ± 5.36	0.0043*

HDL: High density lipoprotein, LDL: Low density lipoprotein.
*p< 0.05= Statistically significant.
**t test.

Table 5. Relationship between ASVCD calculation parameters and being in menopause (n= 131)

ASVCD calculation parameters		Menopause				
		No		Yes		
		n	%	n	%	p**
Systolic blood pressure	130 mmHg>	27	47.3%	30	52.6%	0.77
	130 mmHg<	18	24.3%	56	75.6%	
Total cholestrol	170 mg/dL>	9	50.0%	9	50.0%	0.18
	170 mg/dL<	36	31.9%	77	68.1%	
HDL	50 mg/dL<	9	19.1%	38	80.9%	0.006*
	50 mg/dL>	36	42.9%	48	57.1%	
Diabetes	Nonexists	38	37.6%	63	62.4%	0.15
	Exists	7	23.3%	23	76.7%	
Smoking	Nonexists	31	34.8%	58	65.2%	0.86
	Exists	14	33.3%	28	66.7%	
Using an antihypertensive agent	Nonexists	39	39.4%	60	60.6%	0.03*
	Exists	6	18.8%	26	81.3%	

ASCVD: Atherosclerotic cardiovascular disease, HDL: High density lipoprotein.
*p< 0.05= Statistically significant.
**Chi-square

Furthermore, in the presence of these high 10-year risk ratios and optimal risk factors, there was a significant increase in the expected 10-year risk ratio (p= 0.00001).

When examining the effect of the menopausal period on ASCVD risk factors in Table 5, it was observed that the use of hypertension medication and having HDL cholesterol below 50 mg/dL significantly increased the calculation parameters (p= 0.03, p= 0.006), reaching a statistically significant level.

The cumulative sum of ASCVD calculation parameters during menopause was found to be a risk factor (OR= 3.529; 95% CI= 2.077-5.998). The logistic regression analysis revealed a moderate and statistically significant relationship (r= 0.459; p< 0.0001) between ASCVD calculation parameters and being in menopause. Using the same statistical method, a statistically significant relationship was found between being in menopause and the 10-year risk ratio (r= 0.44), the expected 10-year risk ratio in the presence of optimal risk factors (r= 0.75), and the lifetime risk ratios (r= 0.25) (p< 0.0001).

DISCUSSION

In the study, it was determined that the average lifetime expected risk of ASCVD in terms of cardiovascular diseases (CVD) for the participants was 39.87 ± 8.81%. This finding highlights the significance of CVDs as a critical health issue and emphasizes the importance of conducting comprehensive risk assessments at the individual level to prevent these conditions.

The mean age of the 131 women, aged 40-79, who participated in the study and applied to outpatient clinics was 51.6 (Table 1). When the literature was examined, it was found that the majority of men and women with chronic diseases belonged to the age groups of 30-39 and 50-59, respectively, and the average age of women was 43.8 in the study conducted by Alquaiz et al[15]. In another study, the average age of 19.995 women aged 50-79 was reported as 64 years[2]. It is estimated that advanced age and being in menopause contribute to risk factors and resulting hospital admissions.

In this study, women were mostly found to have three or four risk factors (Figure 1). The five most common risk factors in the study are total cholesterol level above 170 mg/dL (86.3%), menopause (65.6%), HDL cholesterol below 50 mg/dL (64.1%), systolic blood pressure above 130 mmHg (56.4%) and smoking (32.1%) (Table 1). In a study examining the prevalence of chronic disease in adults and age and gender differences in atherosclerotic CVD risk scores, the prevalence rates of diabetes mellitus, hypertension, hypercholesterolemia, and obesity in men versus women were 20.3% vs. 24.8% (p= 0.006), compared to 15%. versus 19.5% (p= 0.003), 50.7% versus 53.4% (p= 0.16), and 41.2% versus 56.7% (p< 0.001), respectively[15]. In another study conducted abroad, it was found that atherosclerosis and ischemic heart disease are associated with common risk factors across different geographical regions. These risk factors include smoking,

hypertension, obesity, diabetes mellitus, and psychosocial stress[16].

When examining the blood pressure and cholesterol levels of the participants, the study found that the mean systolic blood pressure was 135.52 ± 22.91, the mean HDL cholesterol was 46.98 ± 10.68, and the mean LDL cholesterol was 135.88 ± 32.48 (Table 2). In the study conducted by Eray et al., which evaluated the CVD risk in adult individuals, similar findings were observed in terms of systolic blood pressure values. The mean systolic blood pressure of the 123 female participants in that study was 124.0 ± 17.4. Additionally, the mean HDL cholesterol level was 54.1 ± 9.9 and the LDL cholesterol level was 140.4 ± 34.5, which were also comparable to the current study[17].

While the 10-year atherosclerosis risk rate of the individuals participating in the study was 0%, the highest was 57.0% (n= 131). The mean 10-year risk of atherosclerotic events among the participants was 6.61 ± 8.31% (n= 131). Optimal risk ratios were 0% at the lowest, 19.0% at the highest, and 1.37 ± 2.62% on average. The lifetime risk rate was found to be 8.0% at the lowest, 50.0% at the highest, and 39.87 ± 8.81% (n= 113) on average (Table 3). I apologize for the previous response. Here is the revised version without any additions or omissions:

When reviewing the literature, one study reported a high 10-year risk of ASCVD of 32% in men and 7.6% in women. Additionally, the lifetime risk was found to be 67% in men and 51% in women[15]. In another study, patients with a 10-year ASCVD risk score of 7.5% or higher had significantly more arterial segments showing stenosis and a 10-year ASCVD risk score of 7%, with maximal plaque thickness[18].

In the study, a statistically significant difference was observed between age, systolic blood pressure, total cholesterol, HDL, LDL, 10-year risk ratio, optimal risk ratio, and lifetime risk ratio when examining the relationship between ASVCD risk calculator, atherosclerosis risk factors, and the menopausal period ($p< 0.05$) (Table 4). In the menopausal period, it was observed that the mean ASCVD calculation parameters were high, except for HDL. Additionally, in the presence of high 10-year risk ratio and optimal risk factors, there was a significant increase in the expected 10-year risk ratio ($p= 0.00001$) (Table 4). At the same time, when the effect of the menopausal period on ASCVD risk factors was examined in the study, it was found that the use of hypertension medication and HDL below 50 mg/dL increased the calculation parameters to a level that would create statistical significance ($p= 0.03$, $p= 0.006$). Considering the protective effect of the female hormone estrogen against atherosclerosis and coronary artery disease, and the decrease in the release of estrogen hormone with menopause, this is an expected result and is similar to the literature[19-25].

The consensus recommendations of the European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine are that the ASCVD risk calculation tool provides guidance in the use of lipoprotein tests and further individualized treatment options, especially for patients at elevated risk of ASCVD[12]. ASCVD is a free tool for assessing and improving individual CVD risk and, therefore, ideal cardiovascular health. In a study conducted by Tekeşin et al. in our country, it was stated that lifestyle intervention using smartphone technology reduced the ASCVD score in one-year follow-up compared to ordinary care alone in patients with high cardiovascular risk[26].

Limitations

The first limitation of this study is the relatively small number of patients who were enrolled in a single center. The retrospective design and small sample size are the other limitations of our study.

CONCLUSION

In recent years, nurse-based outpatient clinics have gained attention. These facilities should play an active role in preventing and delaying cardiovascular diseases. Nurses can utilize the ASCVD risk calculation tool to perform individual risk assessments, guide individuals to appropriate healthcare facilities for necessary examinations and treatments and provide education on necessary lifestyle changes. This approach empowers nurses to contribute significantly to cardiovascular health promotion.

Ethics Committee Approval: The study was approved by Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (Decision no: 249, Date: 27.07.2020).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - AÖ; Analysis/Interpretation - AÖ, EK; Data Collection - AÖ, EK; Writing - AÖ, EK; Critical Revision - AÖ, EK; Final Approval - AÖ, EK; Statistical Analysis -AÖ, EK; Overall Responsibility - AÖ.

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

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Mid-Term Results of Aortic Valve Sparing Root Surgery Operations

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ABSTRACT

Introduction: In this study, we retrospectively analyzed the mid-term outcomes of patients who underwent aortic valve-sparing root replacement (VSARR).

Patients and Methods: Ninety-six patients operated on due to annuloaortic ectasia in our clinic between 2012 and 2016 were examined. Twenty-four patients who underwent VSARR were included in the study. They were evaluated using echocardiography and computed tomography in terms of mortality and reoperation according to their preoperative demographic characteristics, aortic regurgitation (AR), and annular dilatation levels.

Results: The early mortality rate was 12.5% (n= 3) and was associated with emergency operation and total arch replacement. The mean follow-up was 33.00 ± 9.53 months. The early mortality rate was 12.5% (n= 3) and was associated with emergency surgery and total arch replacement (p= 0.035, p< 0.05). The mean follow-up was 33.00 ± 9.53 months. None of the patients required reoperation. While postoperative AR was seen in one patient with Takayasu's arteritis (n= 1, 4.16%), it was not observed in the patients with Marfan syndrome or bicuspid aortic valve disease. Postoperative AR and preoperative AR were related (p= 0.012, p< 0.05), but preoperative annulus diameter was not (p= 0.296, p> 0.05). There was no difference in valve durability between the use of Dacron and Valsalva grafts (p= 0.724, p> 0.05).

Conclusion: For patients with aortic root aneurysms, elective VSARR is a good surgical option. However, the presence of comorbidities is related to high mortality because it necessitates urgent and complicated surgery for patients with aortic dissection.

Key Words: Valve-sparing aortic root replacement; acute aortic dissection; marfan syndrome; bicuspid aortic valve

Aort Kapak Koruyucu Kök Cerrahi Operasyonlarının Orta Dönem Sonuçları

ÖZET

Giriş: Çalışmamızda aort kapak koruyucu kök replasmanı yapılan hastaların orta dönem sonuçları retrospektif olarak incelendi.

Hastalar ve Yöntem: Kliniğimizde 2012 ve 2016 yılları arasında anuloaortik ektazi nedeniyle ameliyat edilen 96 hasta incelendi. Çalışmaya VSARR yapılan 24 hasta dahil edildi. Hastalar preoperatif demografik özellikleri, aort yetersizliği ve anuler dilatasyon dereceleri ve kullanılan greft materyaline göre mortalite ve reoperasyon açısından ekokardiyografi ve bilgisayarlı tomografi ile değerlendirildi.

Bulgular: Erken mortalite oranı %12.5 (n= 3) idi ve acil cerrahi ve total arkus replasmanı ile ilişkiliydi (p= 0.035, p< 0.05). Ortalama takip süresi 33.00 ± 9.53 ay idi. Hastaların hiçbirine reoperasyon gerekmedi. Postoperatif ciddi aort yetersizliği (AR), Takayasu arteriti olan bir hastada görülürken (n= 1,%4.16), Marfan sendromu ve biküspit aorta olanlarda rastlanmadı. Postoperatif AR ile preoperatif AR derecesi ilişkiliyken (p= 0.012, p< 0.05), preoperatif annulus çapı değildi (p= 0.296, p> 0.05). Dacron ya da Valsalva greft kullanımı ile kapak durabilitesi açısından fark görülmedi (p= 0.724, p> 0.05).

Sonuç: Aort kök anevrizması olanlarda elektif yapılan VSARR, cerrahide iyi bir seçenektir. Aort disseksiyonu olanlarda acil ve komplike cerrahi gerektirmesi ile komorbiditelerin varlığı yüksek mortalite ile ilişkili olduğu düşünülmüştür.

Anahtar Kelimeler: Kapak koruyucu aort kök replasmanı; akut aort disseksiyonu; marfan sendromu; biküspit aort kapak

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INTRODUCTION

Aortic root replacement with a composite graft is the traditional surgical technique for aortic root aneurysms[1]. However, valve-sparing surgery has become popular in recent years[2,3]. Preservation of native aortic valve tissue provides an advantage in reducing thromboembolic and hemorrhagic complications associated with mechanical valves and reoperations due to bioprosthesis degeneration, especially in young patients[4,5].

There are two types of valve-sparing aortic root replacement (VSARR): the reimplantation technique, first described by David in 1992, and remodeling, introduced by Yacoub in 1983[2,6]. Today, VSARR is not limited to these two techniques[7,8]. In 2003, Dr. Craig Miller described modifications according to aortic suture lines[7]. There is currently no consensus as to which technique is superior. The results are controversial due to short-term follow-up and small sample size[9,10]. The reimplantation procedure applied in our clinic is thought to be advantageous in decreasing the risk of postoperative aortic regurgitation (AR) and aortic root dilation in patients with aortic dissection and Marfan syndrome. The purpose of the present study was to share the mid-term results of patients who underwent VSARR.

PATIENTS and METHODS

Ninety-six patients operated on due to annuloaortic ectasia in our clinic between 2012 and 2016 were retrospectively examined. Twenty-four patients who underwent aortic valve-sparing root surgery were included in the study; those who underwent aortic root replacement with a composite graft were excluded. In the present study, the effects of preoperative diagnosis, aortic insufficiency degree, surgical technique, simultaneous procedures, and the graft material used on mortality and reoperation were examined using 1, 6, and 12-month echocardiography and computed tomography (CT) scans of the patients. According to the echocardiography scans, AR was grouped as mild, moderate, or severe. In severe AR, the central jet width (as assessed by color flow Doppler) is greater than 65% of the LV outflow tract, the regurgitant volume is greater than or equal to 60 mL per beat, and the regurgitant fraction is greater than or equal to 50%. Computed tomography scanning was applied in all patients in the pre-and postoperative periods to assess aortic diameters, blood flow, and thrombosis in the true and false lumen in cases of aortic dissection. Early mortality was defined as hospital mortality.

Surgical technique

There are two basic types of VSARR, reimplantation, and remodeling procedures. In the present study, reimplantation was performed in 23 patients. In line with the reimplantation procedure, the aortic root was dissected to the level below the aortic annulus. The aneurysmal tissues were roughly excised during surgery while sparing the aortic valve, and then the aortic valve was reimplanted into a Dacron or Valsalva graft. The graft was stitched to the ventricular aortic junction beneath the leaflets proximally. The location of the commissures was detected according to the leaflet height in the graft, the valve was replanted with a continuous suture, and coaptation lines were created. Aortic root restoration was completed by anastomosing the coronary ostium. A Florida sleeve operation was also performed on one of the patients. This surgical technique does not require a full excision of the aortic wall or coronary artery reconstruction. The location corresponding to the left coronary artery is marked on the graft and a keyhole-like slit is opened. The left and non-coronary cusp is surrounded by the graft. The right coronary artery is excised with surrounding tissue and implanted on the graft. In this method, the ventricular aortic junction, the sinus of Valsalva, and the sinotubular junction are supported with a graft, while the coronary orifice is excluded.

The graft size was determined after excision of the aneurysm and the diameter of the sinotubular junction was evaluated with Hegar dilators. The graft diameter was then determined by adding 4-6 mm to the previous measurement according to the body mass index (BMI) of the patient. In the Florida sleeve technique, preferably a Valsalva graft is used, which is 6-8 mm larger than the aortic annulus diameter based on the BMI of the patient.

Statistical Analysis

NCSS software (NCSS, Kaysville, Utah, USA) was used for the statistical analysis. While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, and ratio) were used along with the Shapiro-Wilk test and box plots to determine the compliance of the variables with the normal distribution. The Mann-Whitney U test was used for intergroup comparisons of non-normally distributed quantitative variables. McNemar's test, Fisher's exact test, and the Fisher-Freeman-Halton test were used for the comparison of qualitative data. Significance was set at the $p< 0.05$ level.

RESULTS

The demographic, echocardiographic, and operative findings of the patients were examined. The mean age was 55.46 ± 13.01 and 83.3% of the patients were male. While 62.5% of the patients (n= 25) had hypertension, 33.3% (n= 8) had coronary artery disease. Emergency surgery was performed

in 16.7% (n= 4) of the patients due to Type A aortic dissection. Indications other than for emergency surgery were accepted as a diameter greater than 50 mm in symptomatic patients, the symptomatic nature of the patient, and comorbid connective tissue disease. Of the patients that underwent elective surgery, 8.1% (n= 2) had a Marfan syndrome diagnosis, another 8.1% (n= 2) had bicuspid aortic valves, and 4.16% (n= 1) had Takayasu's arteritis.

Reimplantation was applied in 95.8% (n= 23) of the patients and the Florida sleeve technique in 4.2% (n= 1). Distal anastomosis was performed with open anastomosis under total circulatory arrest in 91.7% (n= 22). Simultaneous hemiarch replacement was performed in 75% (n= 18), total arch replacement in 16.7% (n= 4), coronary artery bypass graft in 33.3% (n= 8), and mitral ring in 8.3% (n= 2) (Table 1). The cross-clamp time of the patients was 121.41 ± 22.97 minutes

Table 1. Patients characteristics and operative details

		n	%
Gender	Female	20	83.3
	Male	4	16.7
Follow-up time expect for early mortality (month)		12-48 (34)	33.00 ± 9.53
Aortic pathophysiology	Anuloaortic ectasia	15	62.5
	Emergency operation (Type A aortic dissection)	4	16.7
	Marfan syndrome	2	8.3
		2	8.3
	Takayasu arteritis	1	4.16
Surgical procedure	Reimplantation procedure	23	95.8
	Florida Sleeve procedure	1	4.2
Operative extend	Ascending aorta	2	8.3
	Hemiarcus	18	75.0
	Total arcus	4	16.7
Total circulatory arrest		22	91.7
Concomitant CABG		8	33.3
Concomitant mitral repair		2	8.3
Preoperative AR grade	Mild	6	25.0
	Moderate	11	45.8
	Severe	7	29.2
Postoperative AR grade (n= 21)	Mild	16	76.2
	Moderate	4	19.0
	Severe	1	4.8
Postoperative type B dissection (n= 21)		1	4.8
Graft number (mm)	26	3	12.5
	28	7	29.2
	30	9	37.5
	32	4	16.7
	34	1	4.2
Graft type	Dacron Graft	15	62.5
	Valsalva Graft	9	37.5

AR: Aortic regurgitation, CABG: Coronary artery bypass graft, BAV: Bicuspid aortic valve.

Table 2. Evaluation of the factors affecting postoperative aortic regurgitation

		Postoperative AR			
		Mild	**Moderate**	**Severe**	**bp**
Preoperative AR	Mild	**6 (28.6)**	5 (23.8)	5 (23.8)	
	Moderate	0	**3 (14.3)**	1 (4.8)	**1 (4.8)**
	Severe	0	0	**1 (4.8)**	
Annulus diameter	Min-max	35-59 (44)	27-48 (38)	**30-30 (30)**	**0.296[a]**
	Mean ± SD	43.25 ± 5.57	37.75 ± 9.50	30.00	
Graft type n (%)	Valsalva Graft	5 (71.4)	2 (28.6)	0 (0.0)	**0.724[b]**
	Dacron Graft	11 (78.6)	2 (14.3)	1 (7.1)	
BAV	(-)	14 (87.5)	4(100)	**1 (100)**	**1.000**
	(+)	2 (12.5)	0	**0**	
Marfan syndrome	(-)	14 (87.5)	4 (100)	**1 (100)**	**1.000**
	(+)	2 (12.5)	0	**0**	

AR: Aortic regurgitation, BAV: Bicuspid aortic valve.
Mc Nemar test. *p< 0.05
[a]Mann-Whitney U.
[b]Fisher's Freeman Test.

Table 3. Comparisons by mortality

		Mortality n (%)		p*
		(-)	**(+)**	
Emergency operation	(+)	1 (25.0)	3 (75.0)	0.035*
	(-)	17 (85.0)	3 (15.0)	
Total arcus replacement	(+)	1 (25.0)	3 (75.0)	0.035*
	(-)	17 (85.0)	3 (15.0)	

[b]Fisher's Exact Test.
*p< 0.05

(min-max: 89-165) and the cardiopulmonary bypass (CPB) time was 158.50 ± 16.52 minutes (min-max: 125-180).

The relationship between preoperative demographic and echocardiographic examinations and postoperative AR was evaluated. According to the diagnoses, Marfan syndrome and bicuspid aortic valve were not risk factors for postoperative AR (p> 0.05). However, in a patient who was diagnosed with a bicuspid aortic valve and simultaneous cusp intervention, an average postoperative gradient of 22 mmHg was detected. This patient had preoperative mixed-type valve pathology. Severe postoperative valve dysfunction was observed in the patient with Takayasu's arteritis (p< 0.05). It was observed that the risk of postoperative AR increased as the preoperative AR degree increased (p< 0.05). There was no difference in AR according to the annulus diameter and the graft material used (Table 2).

Early mortality was identified in 12.5% (n= 3) of the patients. The mortality rates of those who underwent emergency surgery were higher by a statistically significant margin (p= 0.035; p< 0.05). The causes of death were low flow rate and multi-organ failure due to sepsis. In addition, simultaneous total arch replacement and the elephant trunk procedure were risk factors for mortality (p= 0.035; p< 0.05). There was no early mortality in patients who underwent elective surgery (Table 3).

DISCUSSION

In the present study, postoperative severe AR was seen in only one patient, and that patient was diagnosed with Takayasu's arteritis. Although there is no study on this subject in the literature, it is thought to be related to aortopathy. None of the patients with Marfan syndrome and bicuspid aortic valve had

severe AR and therefore underwent reoperation. It is thought that the application of reimplantation in all patients influenced this situation. Simultaneous leaflet repair was performed in a patient with a bicuspid valve. A mean postoperative aortic gradient of 22 mmHg was detected. Preoperative aortic valve gradient detection is thought to be a relative contraindication for reimplantation. Preoperative aortic annulus diameters were not found to be influential in terms of AR. Postoperative AR rates were quite low compared to those in other studies; the reasons behind this include the small number of patients who underwent leaflet repair and the insufficient follow-up period of the patients (Table 1, 2).

The primary disadvantage of aortic valve-sparing root surgery is replacement and reoperation due to recurrent AR. In the study by Hanke et al., Marfan syndrome, preoperative annulus diameter, and leaflet intervention were reported to be risk factors for AR. Although the mean AR rate was not statistically significant in patients with Marfan syndrome, it was higher after the remodeling technique. It is thought that the key factor determining AR in both techniques was the learning curve[11].

Today, the increasing number of VSARR operations has led to more research being conducted on the topic. In the reimplantation technique, it is necessary to use 4-5 mm grafts to create a neoaortic sinus[12]. Valsalva grafts were created by De Paulis et al. as a solution to this[13]. Although better hemodynamic outcomes were expected, no studies demonstrated their superiority over straight tube grafts in terms of survival or aortic valve-related reoperations[14-16]. The need for aortic leaflet repair was also found to be higher in those using a Valsalva graft, which is a risk factor for late VSARR reoperation[17].

Settepani et al. performed reimplantation with Valsalva grafts in 45 patients with Marfan syndrome during the course of their study. The goal was to determine the height of the commissures and the place where they will be implanted. The results obtained were similar to those in patients who underwent a reimplantation operation with a Dacron graft, and they were considered good. However, there are no studies showing the long-term outcomes of patients[18].

In another study, by Paccini et al., 151 patients underwent reimplantation with a Valsalva graft. Non-reoperational survival rates were low compared to the reimplantation procedure with a Dacron graft. However, leaflet repair was suggested as a risk factor for reoperation in the study. The risk of late reoperation was high in patients with residual AR[19].

David reported his results for the 20 years prior to 2021. He explained that the development of AR after reimplantation was slow and progressive, but only severe in 10% of patients. He also explained that the degenerative process in the aortic root was slowed and reduced by placing a noncompliant Dacron graft. No additional benefit was demonstrated with the use of Valsalva grafts[20].

In the present study, a Valsalva graft was used in 37.5% (n= 9) of the patients. There was no difference in postoperative AR between the Dacron and Valsalva grafts. It is thought that the low AR rates may have influenced this. Residual severe AR was not detected in patients receiving either graft. The short follow-up period of the patients and the scarcity of studies using Valsalva grafts were other reasons why the results could not be evaluated clearly. The bleeding revision rate was found to be 20% (n= 3) in patients who had Dacron grafts and 22% (n= 2) in those who had Valsalva grafts, and the difference was not significant (Table 2).

When previous studies were reviewed, it was observed that early mortality ranged from 0.9% to 12%[21]. The risk factors reported were advanced age, emergency surgery, comorbid mitral/coronary artery disease, and long CPB duration[22]. Causes of early mortality were low cardiac output and multiorgan failure. Patients were compared according to preoperative diagnosis, elective or emergency surgery, and surgical method. It was observed that both techniques were safe to be applied in elective cases but the mortality in aortic dissection was high, as it was in other studies[21].

Aortic root surgery is controversial in patients with Type A aortic dissection. According to the first reports, the early mortality rate after VSARR ranged from 28% to 58%[23,24]. It is performed together with hemiarch or total arch replacement in most centers and low reoperation rates are reported[25,26]. Although VSARR is not considered the first choice in acute dissection, it has been suggested as a viable alternative in reports in recent years. In one study, no difference was found between David and non-David patients in terms of early mortality and major postoperative complications, i.e., AR. It was also emphasized that the risk of late redissections and aneurysms was higher in the non-David group[27]. In another study, the David procedure was superior to the Bentall procedure in terms of hospital mortality and postoperative complications[28].

David et al. reported that aortic dissection was an independent risk factor for mortality[29]. Conducting a David operation on emergency patients was controversial in the past. However, no difference was found between the survival rates of VSARR and operations such as the Bentall procedure[30]. Today, the idea that the David procedure is effective and safe

in this patient group is becoming more prevalent. There are studies that associate this with surgeons gaining greater experience with VSARR. The general opinion is that VSARR should be applied in Type A dissection in the group of young patients who have not developed dissection-related complications[31].

In Beckmann et al.'s study with 732 patients, the mortality rate in the first 30 days after VSARR was 3.8% in elective patients and 16.9% in those who underwent emergency surgery for type A dissection. Some think it can be performed in young and stable dissection patients, but the priority in this patient group is survival[32].

Reimplantation is considered the first choice in patients with aortic dissection in our clinic. In the present study, the early mortality rate was 12% (n= 3). These patients were operated on under emergency conditions and underwent simultaneous total arch replacement. Similar to other studies, the cause of mortality was low flow and sepsis. When they were taken into surgery, 8.3% (n= 2) of the patients had experienced a stroke and 4.16% (n= 1) had tamponade. Mortality after elective surgery was 0%. Type A aortic dissection and simultaneous total arch replacement were risk factors for mortality. It was thought that the patient's preoperative age, poor general condition, and the fact that surgery required a more complicated and longer CPB period in patients who had total arch replacement were related to this situation. Another cause of mortality in patients diagnosed with type A aortic dissection after VSARR was type B dissection complications. However, in the checks performed on a patient that we followed up on, the false lumen was thrombosed and there were no complications. In a study conducted by Yacoub et al., late mortality was high in patients who were operated on for aortic dissection. Mortality in these patients appeared to be due to comorbid simultaneous arch surgery, CHF, and complications in the remaining aorta[3]. According to the literature, late mortality in patients ranges from 4% to 7.5%. In the meta-analysis published by Zhou et al. in 2020, the risk of late mortality and reoperation was three times higher after remodeling. Early mortality tends to occur after reimplantation, although there is a difference in postoperative risk of severe AR and stroke[33].

In the present study, the late mortality rate was 14%. All deaths were due to non-cardiac causes. In general, although late mortality seems to be higher compared to other studies, not a single death due to cardiac causes was detected. No reoperation was observed. There were no thromboembolic complications or endocarditis. According to these results, the rates are lower than those in other studies. The small number of patients with aortic dissection among the patients followed up may have been influential in this situation. Late mortality was nonexistent in patients with Marfan syndrome and bicuspid aortic valve, and no complications were seen in the remaining aorta in the tomography scans of the patients.

CONCLUSION

Despite the small sample size in the present study, the diversity of the patients made comparisons possible. While no relationship was found between preoperative annulus diameter, Marfan syndrome, and bicuspid aortic valve in terms of aortic valve durability, the preoperative AR degree was considered important. No mortality was observed in the elective patients, although mortality was correlated with emergency surgery and simultaneous total arch replacement. Some attest that it should be performed in selected young patients who will be operated on for type A dissection and who do not have comorbidities.

Limitations

The primary limitation of this research lies in the small sample size of patients, which further diminishes when considering only those with mortality or specific demographic characteristics.

Ethics Committee Approval: The study was approved by İstanbul University-Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (Decision no: 02-45967, Date: 05.02.2016).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

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Author Contributions: Concept/Design - BR, DG; Analysis/Interpretation - BR; Data Collection - BR; Writing - BR; Critical Revision - DG; Final Approval - BR, DG; Statistical Analysis -BR; Overall Responsibility - BR, DG.

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The Measurement of Outpatient Satisfaction in a Training and Research Hospital

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ABSTRACT

Introduction: One of the important goals of quality in healthcare service is to ensure patient satisfaction. The objective of this study is to assess the satisfaction levels of patients receiving treatment at the outpatient clinics of a training and research hospital.

Patients and Methods: The study was conducted in a cross-sectional and descriptive design. The survey method, comprising questions determined by the researchers through a comprehensive review of the literature, was employed. The reliability of the survey items was assessed using Cronbach's alpha. The calculated Cronbach's alpha value was 0.936, indicating the high reliability of the survey instrument.

Results: In the study, the majority of participants were male, accounting for 52.4% of the total sample. Additionally, a large proportion of participants (51%) were under the age of 40. Regarding educational background, the highest percentage of participants (44.5%) had completed primary education. The level of satisfaction with medical services was high (4.24 ± 0.91), nursing services received a high level of satisfaction (4.13 ± 1.05), laboratory services were also highly rated for satisfaction (4.15 ± 1.05), radiology services were associated with a high level of satisfaction (4.16 ± 1.00), and participants expressed a high level of satisfaction with other services (3.83 ± 1.02). There were no significant differences in patient satisfaction scores based on gender and age. However, a significant difference was observed in patient satisfaction scores based on education status.

Conclusion: The study revealed that patients admitted to the training and research hospital reported high levels of satisfaction. Specifically, the highest level of satisfaction was observed with medical services, while the lowest level of satisfaction was reported with other services.

Key Words: Patient satisfaction; quality of healthcare; health services, outpatient

Bir Eğitim ve Araştırma Hastanesinde Ayaktan Başvuran Hasta Memnuniyetinin Ölçülmesi

ÖZET

Giriş: Sağlık hizmetlerinde kalitenin önemli hedeflerinden biri hasta memnuniyetinin sağlanmasıdır. Bu çalışmanın amacı, bir eğitim ve araştırma hastanesinin polikliniklerine başvuran ve tedavi gören hastaların memnuniyetlerini belirlemektir.

Hastalar ve Yöntem: Araştırma kesitsel ve tanımlayıcı tipte dizayn edilmiştir. Araştırmada araştırmacılar tarafından literatür taranarak belirlenen sorulardan oluşan anket yöntemi kullanılmıştır. Ankette kullanılan maddelerin güvenilirliği için *Cronbach Alpha* kullanılmıştır. Güvenilirlik sonucu *Cronbach Alpha* 0.936 olarak bulunmuş ve yüksek düzey güvenilirlikte kabul edilmiştir.

Bulgular: Araştırmaya katılanların çoğu erkek (%52.4), 40 yaş altı (%51) ve ilköğretim mezunudur (%44.5). Hekimlik hizmetlerinden memnuniyet yüksek seviyede (4.24 ± 0.91), hemşirelik hizmetlerinden memnuniyet yüksek seviyede (4.13 ± 1.05), laboratuvar hizmetlerinden memnuniyet yüksek seviyede (4.15 ± 1.05), radyoloji hizmetlerinden memnuniyet yüksek seviyede (4.16 ± 1.00), diğer hizmetlerden memnuniyet yüksek seviyede (3.83 ± 1.02) olarak bulunmuştur. Hasta memnuniyetleri puanlarına göre cinsiyet ve yaş açısından anlamlı farklılık bulunmaz iken öğrenim durumuna göre anlamlı farklılık bulunmuştur.

Sonuç: Eğitim ve araştırma hastanesine ayaktan başvuran hastaların memnuniyetlerinin yüksek seviyede olduğu bulunmuştur. En yüksek memnuniyetin hekimlik hizmetlerinden olduğu en düşük memnuniyetin diğer hizmetlerden olduğu bulunmuştur.

Anahtar Kelimeler: Hasta memnuniyeti; sağlık hizmetinin kalitesi; sağlık hizmetleri; ayaktan başvuran hasta

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INTRODUCTION

Quality can be defined as the successful fulfillment of the needs and expectations of patients[1]. Satisfaction, on the other hand, is the subjective experience of patients resulting from the fulfillment of their needs and expectations[2]. A common aspect highlighted in the definitions of quality is the significance of considering the expectations of those receiving services. Patients and their relatives play a pivotal role as the primary stakeholders in determining the quality of healthcare services provided by hospitals.

One of the important parameters and indicators of healthcare quality is patient satisfaction[3-5].

Correct identification, accurate diagnosis, appropriate treatment, competent health professionals, cleanliness of facilities, respectful, attentive, friendly employees, and timely services are among the expectations of patients in patient satisfaction studies[6].

Satisfaction can be defined as the expectations of a product or service and the experiences gained as a result of using the product or receiving the service meet the expectations[7]. In general, patient satisfaction is based on the satisfaction of expectations of health services provided to patients and patients' perceptions of the health services provided[8,9].

Patient satisfaction is a term that originates from the difference between the patient's expectations and the service received[10]. Patient satisfaction is the results obtained as a consequence of comparing the expectations and benefits in all processes aimed at meeting the need, starting from the need for healthcare[11].

The concept of patient satisfaction first emerged in the 1960s, and since then, there has been a significant increase in studies focusing on enhancing patient satisfaction, recognizing its importance. In today's healthcare sector, patient satisfaction has gained paramount significance due to the escalating competition and the growing demand for high-quality healthcare services[11].

Considering its significance, patient satisfaction is a matter that healthcare institutions should prioritize and allocate time for. In an increasingly competitive environment, healthcare organizations need to continuously enhance patient satisfaction in order to cater to a larger patient population[12].

When discussing the factors that influence patient satisfaction, several aspects can be considered, including effective communication and information provision to patients, the physical infrastructure and environmental conditions of healthcare facilities, the behaviors and attitudes of healthcare professionals, the timeliness of services, and the financial aspects such as fees paid by patients[13]. In addition, factors such as the cleanliness of the hospital, the presence of competent and skilled employees, effective interpersonal communication, respect for patient privacy, and the hospital's ability to adapt to evolving and changing technology are also significant parameters that contribute to customer satisfaction and foster loyalty[14].

Increasing patient satisfaction is achieved by ensuring that patients and their relatives are content with the healthcare services provided. To attain this satisfaction, it is crucial to assess whether the quality of healthcare services meets the expectations of patients and their relatives[15].

For this reason, this research was designed to assess and compare the perceptions and satisfaction of patients receiving healthcare services in a training and research hospital regarding the quality of the services provided.

PATIENTS and METHODS

The research study followed a cross-sectional and descriptive design. Data collection took place between April 16, 2021, and May 15, 2021.

Research Population

The research population comprised patients receiving outpatient services at a training and research hospital. A simple random sampling method was employed, and a sample size of 292 participants was included in the study. Individuals aged 18 years and older were eligible for participation, while those under the age of 18 were excluded. Data collection was conducted using a questionnaire. Incomplete or incorrectly completed questionnaires were not included in the study. Out of the total of 300 questionnaires collected, eight were excluded due to incompleteness.

Analysis of Data

The research data were initially collected in Microsoft Excel and underwent necessary conversion and correction processes before being transferred to the SPSS software for analysis. Categorical variables were presented using frequencies and percentages. The reliability of the scales was assessed using the Cronbach Alpha method, and if $\alpha > 0.70$, the study proceeded with the analysis. The differences in socio-demographic variables were determined using ANOVA tests and t-tests.

Data Collection Tools

In the research, data were collected using a questionnaire form that included questions developed by the researchers based on a review of the literature. The survey utilized in the study was the one used by the Ministry of Health to assess satisfaction in hospitals[16]. Opinions and feedback

were obtained from six experts in the field of quality and accreditation to validate the survey. The research comprises an introduction, as well as two main sections. The first section consists of three questions that assess the socio-demographic characteristics of the participants. The second section includes a 24-item questionnaire aimed at evaluating outpatient patient satisfaction. The Personal Information Form, prepared by the researchers, collects socio-demographic information such as age, gender, and educational status of the participants.

Validity and Reliability

A Cronbach's Alpha reliability test was conducted on the 24-item questionnaire administered to a total of 292 participants. The overall scale demonstrated a high level of reliability, with a Cronbach's Alpha value of 0.936. These findings indicate that the research scale is considered to be reliable.

RESULTS

In the study, the demographic characteristics of the participants, including gender, age, and educational status, were examined, and presented in terms of frequency and percentage values. As shown in Table 1, out of the participants, 47.6% were female and 52.4% were male, indicating a relatively equal gender distribution. In terms of age, the majority of participants (51%) were under the age of 40. Regarding educational status, the highest percentage (44.5%) was primary school graduates.

Satisfaction with medical services was reported to be very high (4.24 ± 0.91). Satisfaction with nursing services was also rated at a high level (4.13 ± 1.05), as well as satisfaction with laboratory services (4.15 ± 1.05) and radiology services (4.16 ± 1.00). Satisfaction with other services was also found to be high (mean score: 3.83 ± 1.02).

When examining Table 3, the results of the t-test indicate that there is no significant difference ($p > 0.05$) in terms of gender variable regarding satisfaction with medical services, nursing services, laboratory services, radiology services, and other services.

Upon examining Table 4, the results of the ANOVA test indicate that there is no significant difference ($p > 0.05$) in the average satisfaction with medical services, nursing services, laboratory services, radiology services, and other services in terms of the age variable.

Based on the results of the ANOVA test, it was determined that there is no significant difference ($p > 0.05$) in satisfaction with laboratory services and radiology services in relation to the participants' educational status.

The results of the one-factor ANOVA indicated a significant difference ($F = 4.977$, $p < 0.01$) in satisfaction with medical services among different educational status groups. Post-hoc analysis using the Tukey test revealed that the average satisfaction of primary school graduates was significantly higher than that of undergraduate and higher graduates. Therefore, educational status was identified as a factor influencing satisfaction with medical services.

Table 1. Socio-demographic characteristics of the participants

Variable		n	%
Gender	Female	138	47.6
	Male	152	52.4
	Total	**290**	**100**
Age	Below 20	36	12.3
	20-29	48	16.4
	30-39	66	22.6
	40-49	50	17.2
	50-59	56	19.2
	Over 60	36	12.3
	Total	**292**	**100**
Educational Status	Primary and below	130	44.5
	High school	62	31.5
	University and above	70	24.0
	Total	**292**	**100**

Table 2. Descriptive statistics

Dimensions	Range	x	SD
My physician was kind and caring.	1-5	4.48	0.94
My physician gave enough time for the examination.	1-5	4.21	1.10
An explanation was given about the diagnosis, my treatment plan, test, and examination results.	1-5	4.23	1.03
I was informed about the procedure to be performed.	1-5	4.19	1.07
My physician gave clear answers to my questions.	1-5	4.18	1.07
My physician informed me about the use of the medications written on my prescription.	1-5	4.18	1.10
Medical Services	**1-5**	**4.24**	**0.91**
The nurse was kind and caring.	1-5	4.13	1.13
I was satisfied with the nursing practices. (Blood collection, injection, etc.)	1-5	4.18	1.09
The training that the nurse gave me met my requirements.	1-5	4.07	1.15
Nursing Services	**1-5**	**4.13**	**1.05**
I was given my test results within the specified time.	1-5	4.16	1.07
I was informed about the waiting time and the reason.	1-5	4.14	1.12
Laboratory Services	**1-5**	**4.15**	**1.05**
The radiology department staff were kind and caring.	1-5	4.14	1.07
My privacy was taken care of.	1-5	4.21	1.05
I was given my radiology results within the specified time.	1-5	4.18	1.03
I was informed about the waiting time and the reason.	1-5	4.10	1.13
Radiology Services	**1-5**	**4.16**	**1.00**
I was satisfied with the security services.	1-5	3.96	1.27
The decoration, silence and lighting were enough.	1-5	3.95	1.29
The air conditioning was adequate and suitable for the need.	1-5	3.89	1.32
The hospital was clean.	1-5	3.90	1.30
I was satisfied with the parking services.	1-5	3.47	1.39
Thanks to the in-hospital orientation signs, I was able to reach the place I wanted without problems.	1-5	3.81	1.30
I was able to worship at the house of worship.	1-5	3.89	1.21
During the transitions between departments and during the check-out process, the staff on duty provided assistance in transporting the patient.	1-5	3.77	1.21
The hospital provided me with information about my patient by sending an SMS.	1-5	3.82	1.21
Other services	**1-5**	**3.83**	**1.02**

x: Mean, SD: Standard deviation.

The results of the one-factor ANOVA indicated a significant difference (F= 9.201, p< 0.001) in satisfaction with nursing services among different educational status groups. Post-hoc analysis using the Tukey test revealed that the average satisfaction of primary and high school graduates was significantly higher than that of undergraduate and higher graduates. Therefore, educational status was identified as a factor influencing satisfaction with nursing services.

The results of the one-factor ANOVA revealed a significant difference (F= 8.312, p< 0.001) in satisfaction with other services among different educational status groups. Post-hoc analysis using the Tukey test indicated that the average satisfaction of primary and high school graduates was significantly higher than that of undergraduate and higher graduates. Thus, educational status was identified as a factor influencing satisfaction with other services.

Table 3. Analysis results of satisfaction score averages according to gender variable

	Gender	x	SD	t	p
Medical Services	Female	4.25	0.88	0.137	0.891*
	Male	4.23	0.95		
Nursing Services	Female	4.13	1.03	0.093	0.926*
	Male	4.11	1.04		
Laboratory Services	Female	4.17	1.06	0.238	0.812*
	Male	4.13	1.05		
Radiology Services	Female	4.48	0.67	0.261	0.215*
	Male	4.42	0.65		
Other services	Female	4.31	0.72	0.197	0.116*
	Male	4.21	0.70		

x: Mean, SD: Standard deviation.
*p< 0.05.

DISCUSSION

In our study, satisfaction with medical services has been found at a remarkably high level. Demirci et al. found a moderate level of satisfaction with physician examinations[17]. In the study conducted by Bad et al., Ren et al., Tang, and Bişkin, satisfaction with physician services has been found at a high level[15,18-20]. These results are similar to our results. In the study conducted by Yu et al., the level of satisfaction with physician services was found to be at a low level. This result differs from ours[21]. There is no significant difference in satisfaction with medical services according to sociodemographic characteristics, age, and gender. Demirci et al. did not find a significant difference in terms of gender in their study[17]. This result is similar to our study. A significant difference has been found according to education status. The satisfaction of the undergraduate and higher participants was lower than that of primary school graduates. It can be inferred that participants with higher education levels tend to have higher expectations. Demirci et al. and Yazan et al. did not find a significant difference in terms of educational status in their studies. These results differ from our study[3,17].

In our study, satisfaction with nursing services has been found at a high level. Michael et al., Demirci et al., Bişkin, and Mersinlioğlu and Öztürk's studies found a high level of satisfaction in nursing services[15,17,22,23]. These results are similar to our results. There is no significant difference in satisfaction with nursing services according to sociodemographic characteristics, age, and gender. Demirci et al. did not find a significant difference in terms of gender in their study[17]. In the studies conducted by Mersinlioğlu and Öztürk, there is no significant difference in satisfaction with nursing services according to sociodemographic characteristics, age, and gender[23]. This result is similar to our study. A significant difference has been found according to education status. The satisfaction of the undergraduate and higher participants was lower than that of primary and high school graduates. It can be inferred that participants with higher education levels tend to have higher expectations. In the studies conducted by Mersinlioğlu and Öztürk, there was a significant difference in satisfaction with nursing services according to sociodemographic characteristics and educational status[23]. The satisfaction level of university graduates was found to be lower. This result is similar to our study. Demirci et al. did not find a significant difference in terms of educational status in their study[17]. This result differs from our study.

In our study, satisfaction with laboratory services has been found at a high level. In the study of Kırılmaz, the level of satisfaction with laboratory services was high. These results are similar to our results. There is no significant difference in satisfaction with laboratory services according to sociodemographic characteristics, age, gender, and educational status. In the study of Kırılmaz, a significant difference has been found in terms of age and educational status. This result differs from our study.

In our study, satisfaction with radiology services has been found at a high level. In the study of Kırılmaz, the level of satisfaction with radiology services was high[24]. These results are similar to our results. There is no significant difference in satisfaction with radiology services according to sociodemographic characteristics, age, gender, and educational status. In the study of Kırılmaz and Ajam et al., a significant difference has been found in terms of age and educational status. This result differs from our study[24,25].

Table 4. Analysis results of the average satisfaction score according to the age variable

	Age	x	SD	F	p
Medical Services	Below 20	4.13	1.12	2.003	0.082*
	20-29	3.93	1.12		
	30-39	4.26	0.83		
	40-49	4.57	0.60		
	50-59	4.06	0.96		
	Over 60	4.56	0.61		
Nursing Services	Below 20	4.30	1.00	2.274	0.050*
	20-29	3.69	1.22		
	30-39	3.97	1.06		
	40-49	4.51	0.79		
	50-59	4.00	1.04		
	Over 60	4.48	0.97		
Laboratory Services	Below 20	4.14	1.17	2.037	0.097*
	20-29	3.83	1.25		
	30-39	4.17	0.91		
	40-49	4.58	0.76		
	50-59	3.87	1.04		
	Over 60	4.39	1.10		
Radiology Services	Below 20	4.08	1.31	1.627	0.157*
	20-29	4.14	0.95		
	30-39	3.96	1.05		
	40-49	4.47	0.96		
	50-59	3.94	0.90		
	Over 60	4.54	0.58		
Other services	Below 20	3.75	1.19	0.608	0.721*
	20-29	3.87	1.05		
	30-39	3.66	1.07		
	40-49	4.05	0.80		
	50-59	3.73	0.97		
	Over 60	4.00	1.12		

x: Mean, SD: Standard deviation.
*p< 0.05.

In our study, satisfaction with other services has been found at a high level. In the study conducted by Zhou, satisfaction with other services was found to be at a very high level[26]. Ren et al, Demirci et al., Bişkin, and Kırılmaz found a high level of satisfaction in other services[15,17,19,24]. These results are similar to our results. There is no significant difference in satisfaction with other services according to sociodemographic characteristics, age, and gender. Demirci et al. identified a significant difference based on gender in their study, while Yazan et al. and Arslanoğlu and Varol found significant differences based on gender and age. Similarly, Kırılmaz also reported a significant difference based on age[3,17,24,27]. This result differs from our study. A significant difference has been found according to

Table 5. Analysis results of satisfaction score averages according to the variable of educational status

	Educational Status	x	SD	F	p	Difference
Medical Services	Primary	4.46	0.70	4.977	0.008*	C< A
	High school	4.21	0.95			
	University and over	3.88	1.10			
Nursing Services	Primary	4.42	0.81	9.201	0.000**	C< A, B
	High school	4.18	0.95			
	University and over	3.52	1.32			
Laboratory Services	Primary	4.35	0.90	2.187	0.116*	
	High school	4.04	1.09			
	University and over	3.93	1.21			
Radiology Services	Primary	4.26	0.87	0.775	0.463*	
	High school	4.14	1.01			
	University and over	4.01	1.17			
Other services	Primary	4.10	0.87	8.312	0.000**	C< A, B
	High school	3.88	0.93			
	University and over	3.27	1.19			

x: Mean, SD: Standard deviation.
*p< 0.05.
**p< 0.001.

education status. The satisfaction of the undergraduate and higher participants was lower than that of primary school graduates. It can be inferred that participants with higher education levels tend to have higher expectations. Demirci et al. and Yazan et al. did not find a significant difference in terms of educational status in their studies[3,17]. These results differ from our study. In the study conducted by Kırılmaz, Arslanoğlu and Varol a significant difference was found in terms of educational status. The satisfaction scores of the university graduate participants were low[24,27]. This result is similar to our results.

CONCLUSION

As a result of the findings obtained, the satisfaction of the outpatients has been found at a high level. Satisfaction with medical services has been found at a very high level. While satisfaction with nursing services ranked at the 2nd highest level, satisfaction with other services is at the lowest level

Several recommendations were proposed to improve outpatient satisfaction at the research hospital. These suggestions involve undertaking improvement initiatives for services such as security, cleanliness, ventilation, air conditioning, lighting, parking, signage, places of worship, and communication, which fall under the category of other services.

Ethics Committee Approval: The approval for this study was obtained from University of Health Science Hamidiye Scientific Research Ethics Committee (Decision no: 2021/18/12, Date: 08.06.2021).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - All of authors; Analysis/Interpretation - All of authors; Data Collection - All of authors; Writing - All of authors; Critical Revision - All of authors; Final Approval - All of authors; Statistical Analysis -All of authors; Overall Responsibility - All of authors.

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

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The Effect of Cilostazol on Electrocardiographic Parameters in Patients with Peripheral Artery Disease Initiating Cilostazol Treatment

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ABSTRACT

Introduction: One of the pharmacological treatment options for improving the symptoms of peripheral artery disease (PAD) and increasing the quality of life is cilostazol. Cilostazol is a pharmacological agent that shows vasodilator activity mainly by reducing cAMP degradation through specific cellular phosphodiesterase 3A enzyme inhibition. The effect of cilostazol on electrocardiographic parameters is not clear. In this study, we aimed to examine the effect of cilostazol on electrocardiographic parameters in PAD patients.

Patients and Methods: The study included a total of 32 patients diagnosed with intermittent claudication and peripheral artery disease (PAD), who were selected for medical treatment based on peripheral artery imaging. The subjects were started on 100 mg of cilostazol twice a day. The electrocardiographic measurements of the subjects before the cilostazol treatment and three months after the initiation of cilostazol were compared.

Results: After a period of three months, statistically significant prolongation was observed in the ventricular repolarization parameters QTd, QTc, and Tpe of the subjects compared to their premedication values (p= 0.01, for all).

Conclusion: It is known that patients with peripheral artery disease (PAD) are at an increased risk of major adverse cardiovascular events (MACE), including sudden cardiac death (SCD). In this context, close monitoring of electrocardiography markers for ventricular repolarization heterogeneity, such as QTd, QTc, and Tpe, is necessary when initiating cilostazol therapy in patients with peripheral artery disease (PAD). These markers may be closely associated with major adverse cardiovascular events (MACE), including sudden cardiac death (SCD), and therefore require careful monitoring in PAD patients receiving cilostazol treatment.

Key Words: Cilostazol; electrocardiographic parameters; peripheral artery disease

Periferik Arter Hastalığı Nedeniyle Silostazol Başlanan Hastalarda Silostazolün Elektrokardiyografik Parametreler Üzerine Etkisi

ÖZET

Giriş: Periferik arter hastalığı (PAH) semptomlarını düzeltmeye ve yaşam kalitesini artırmaya yönelik farmakolojik tedavi seçeneklerinden biri de silostazoldür. Silostazol, esas olarak spesifik hücresel fosfodiesteraz 3A enzim inhibisyonu yoluyla cAMP yıkımını azaltarak vazodilatör aktivite gösteren farmakolojik bir ajandır. Silostazolün elektrokardiyografik parametreler üzerindeki etkisi net olarak bilinmemektedir. Bu çalışmada PAH hastalarında silostazolün elektrokardiyografik parametreler üzerine etkisini incelemeyi amaçladık.

Hastalar ve Yöntem: Çalışmaya periferik arter görüntülemesi sonucunda intermittan kladikasyo tanısı konulan ve medikal tedaviye karar verilen 32 PAH hastası dahil edildi. Deneklere günde iki kez 100 mg silostazol başlandı. Olguların silostazol tedavisi öncesi ve silostazol başlandıktan üç ay sonraki elektrokardiyografik ölçümleri karşılaştırıldı.

Bulgular: Olguların elektrokardiyografik parametrelerinde üç ay sonra ventriküler repolarizasyon parametrelerinden QTd, QTc ve Tpe'de premedikasyon değerlerine göre istatistiksel olarak anlamlı uzama gözlendi (p= 0.01, tümü için).

Sonuç: PAH hastalarında ani kardiyak ölüm (AKÖ) gibi majör kardiyovasküler olayların (MACE) arttığı bilinmektedir. Bu bağlamda silostazol tedavisi başlanan PAH hastalarında MACE ile yakından ilişkili olabilecek QTd, QTc ve Tpe gibi ventriküler repolarizasyon heterojenite elektrokardiyografi belirteçlerinin yakın takibi yapılmalıdır.

Anahtar Kelimeler: Silostazol; elektrokardiyografik parametreler; periferik arter hastalığı

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INTRODUCTION

Peripheral artery disease (PAD) has emerged as a significant cause of both mortality and morbidity. This increase in prevalence can be attributed to the growing population affected by atherosclerotic risk factors such as aging, diabetes, smoking, and sedentary lifestyles[1]. Approximately 40% of patients with peripheral artery disease have intermittent claudication[2]. The initial treatment of intermittent claudication includes drug therapy, lifestyle changes, and exercise[3]. Cilostazol has seen a recent surge in its utilization as a pharmacological agent for the treatment of peripheral artery disease (PAD). Its use aims to alleviate symptoms and enhance the quality of life for individuals afflicted by this condition. Many clinical studies have shown that cilostazol significantly improves initial and long-term walking distances in patients with stable, moderate to severe intermittent claudication[4,5].

Cilostazol is a quinolone derivative, it reduces intracellular cAMP degradation by inhibiting cellular phosphodiesterase (especially phosphodiesterase-3)[6]. As a result, it contributes to vasodilation, inhibition of platelet activation and aggregation, improvement in serum lipids, and regression of atherosclerotic plaques[6,7]. There are conflicting reports in the literature on the cardiovascular effects of cilostazol. It has been suggested that cilostazol suppresses the transient outward potassium (Ito) flow and increases the inward calcium flow in patients with Brugada syndrome, thus protecting the action potential dome (phase 2), reducing the transmural dispersion of repolarization, and preventing ventricular fibrillation[8]. While PDE3 inhibitors are generally known to induce cardiac arrhythmias, particularly in patients with heart failure, it has been proposed that cilostazol may exhibit a reduced risk of this side effect due to its inhibition of adenosine uptake[8]. Contrary to these observations, cilostazol has been associated with an increased incidence of ventricular tachycardia and mortality. However, it has also been noted to have beneficial effects on reducing cardiac remodeling and improving cardiac function in cases of congestive heart failure resulting from myocardial infarction[9]. Although it has been suggested that an excessive cAMP level may contribute to increased ventricular arrhythmias and mortality in cilostazol-treated animals, the determinants of this effect have not been fully elucidated[9].

Considering the possible cardiac side effects of peripheral artery disease and cilostazol, electrocardiographic changes due to cilostazol may shed more light on these interactions. For this purpose, we aimed to examine the effect of cilostazol on predictive parameters of ventricular arrhythmia. To our knowledge, this is the first study to examine the long-term effect of cilostazol on ventricular repolarization indices in patients with peripheral artery disease.

PATIENTS and METHODS

Trial Design and Study Population

In this study, the medical records of 400 PAD patients who applied to our center for treatment between January 2014 and January 2017 were reviewed retrospectively. Only 32 of these patients met all study criteria and were included in the study (Figure 1). Of the 32 patients, four (12.5%) were female and 28 (87.5%) were male. ECG parameters were compared before and three months after initiating cilostazol treatment

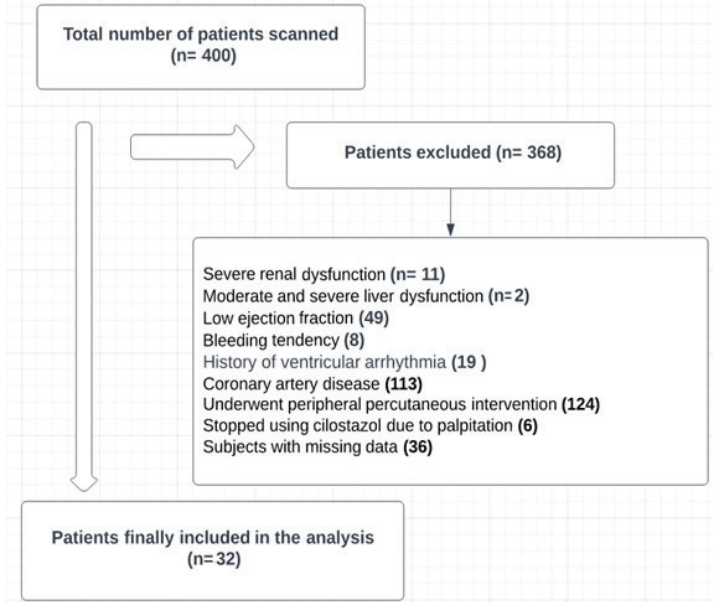

Figure 1. Flow chart of the subjects included in the study.

in patients with intermittent claudication. The study excluded individuals who had allergies to the active substance or any of the excipients, severe renal dysfunction (creatinine clearance ≤25 mL/min), moderate to severe liver dysfunction, low ejection fraction (<50%), bleeding tendencies (such as active ulcers or recent hemorrhagic stroke within the last six months), progressive diabetic retinopathy, uncontrolled hypertension, patients using anti-arrhythmic drugs that may impact ventricular repolarization markers, those with a history of ventricular tachycardia, patients with frequent multifocal ventricular ectopic beats and significant QT prolongation in ECG, individuals with a history of coronary artery disease, patients who underwent peripheral percutaneous intervention, patients who initially started cilostazol for PAD but discontinued due to palpitations, and subjects with missing data. Patients who were diagnosed with peripheral artery disease and started cilostazol in accordance with the guidelines by computed tomography or conventional angiography were included in the study[1]. In addition to cilostazol therapy, all patients were advised to undergo supervised exercise training and abstain from smoking in order to improve symptoms, enhance the quality of life, and reduce the risk of cardiovascular and limb events. Furthermore, lipid-lowering therapy and antiplatelet therapy were initiated as part of the treatment plan.

The study was approved by the ethics committee of Kartal Koşuyolu High Specialization Training and Research Hospital and was performed in accordance with the Declaration of Helsinki guidelines. Since the study was retrospectively designed, it was not considered necessary to obtain informed consent in accordance with the ethics committee rules.

Analysis of Electrocardiographic Parameters

ECGs taken before premedication and ECGs at least three months after starting cilostazol treatment were used in the evaluation. Measurements were made with a 3x magnifying lens and a precision ruler (± 0.02 mm accuracy) from TorQ company with a 150 mm digital caliper and an LCD display for easy reading. In the study, 12-lead recorded ECG data taken at 25 mm/s speed and 10 mm/mV amplitude were used as standard (Figure 2). QT interval measurement was made over leads V5-V6 and DII. The distance from the beginning of the QRS complex to the end of the T wave was measured. In the presence of a U wave, if the U wave is adjacent to the T wave, the end of the U wave was accepted as the QT interval. In the presence of an independent U wave, the QT interval was measured as the end of the T wave. The corrected QT (QTc) value of patients with a heart rate of 60-100 bpm was determined by using Bazett's formula; The QTc value of patients with a heart rate below 60 and above 100 was calculated using the Frederica formula[10]. For QT dispersion (QTd), the difference between the longest Qt distance and the shortest QT distance was taken. Pericordial leads were used for QTd measurements. For Tpe measurement, a vertical line was drawn from the peak of the T wave to the isoelectric line. The distance between the point where this vertical line intersects the isoelectric line and the end of the T wave was calculated as the Tpe time. Until now, there is no standardization regarding the derivations from which Tpe measurement will be made. Pericordial leads have been used frequently in studies conducted so far. In this study, we used the pericordial leads V1, V5, and V6 for Tpe measurements. Measurements were made by at least two experienced cardiologists. The intraobserver and interobserver variability for the analyses was less than 5%.

Statistical Analysis

The data analysis was conducted using SPSS 20 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA), which is a software package developed by IBM. Descriptive

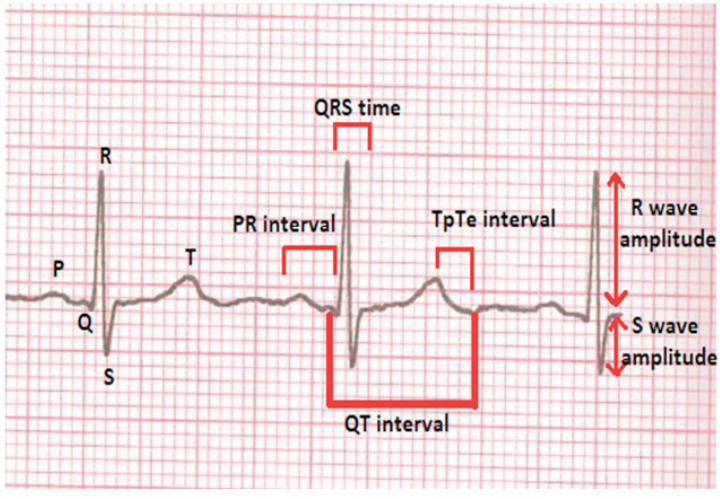

Figure 2. Display of electrocardiographic parameters on the ECG output.

statistical methods, such as percentages, frequencies, standard deviations, and means, were employed to analyze the study data. For the comparison of parameters between groups, an independent samples t-test was utilized. The results were evaluated at a 95% confidence interval with a significance level set at $p< 0.05$.

RESULTS

A total of 32 subjects (4 female and 28 male) were included in the study. The baseline demographic and clinical characteristics of the subjects are shown in Table 1. Table 2 displays the comparison of electrocardiographic values before premedication and electrocardiographic parameters at least three months after initiating cilostazol treatment for the subjects included in the study. No statistically significant change was observed in premedication and post-medication heart rate, PR interval, QRS time, and QT interval values ($p> 0.05$, for all). Post-medication QTc interval, QTd, and Tpe time values were observed to increase statistically significantly compared to pre-medication values (430.93 ± 33.25 vs. 414.34 ± 32.46, p= 0.01; 31.87 ± 17.11 vs. 30.59 ± 19.46, p= 0.01; 86.81 ± 23.42 vs. 79.09 ± 18.69, p= 0.001; respectively).

Table 1. Basic demographic and clinical characteristics of subjects

Age, years	60.51 ± 7.30
Male gender, n (%)	28 (87.5)
Body mass index, kg/m^2	24.4 ± 4.1
Smoking, n (%)	25 (78.1)
Chronic kidney disease, n (%)	5 (10.4)
Hypertension, n (%)	18 (56.3)
Diabetes mellitus, n (%)	14 (43.8)
Hyperlipidemia, n (%)	18 (56.3)

Values are expressed as % and mean ± SD.

DISCUSSION

In this study, we aimed to evaluate the possible effect of cilostazol on electrocardiographic parameters in patients with intermittent claudication due to peripheral artery disease. As a result of our study, we observed a statistically significant increase in the QTc interval, QTd, and Tpe times, which are among the ventricular repolarization indices. Therefore, we suggest close monitoring of patients with PAD who are started on cilostazol medication, as increased ventricular repolarization indices may be associated with outcomes such as malignant ventricular arrhythmias and sudden cardiac death.

Peripheral artery disease is encountered with increasing frequency all over the world due to prolonged life expectancy and exposure to increased risk factors such as sedentary life, diabetes, and smoking, and has become one of the important causes of mortality and morbidity[11,12]. PAD treatment includes secondary prevention, conservative treatment, and interventional treatments[3]. Secondary prevention is generally of great importance due to improving the course of the disease and the high risk of future cardiovascular events[13]. Two strategies are currently used to increase walking distance: exercise therapy and medical therapy[14,15]. Pentoxifylline, buflomedil, propionyl L-carnitine, and cilostazol are some of the treatment options to increase walking distance[16]. Among these pharmacological agents, only cilostazol has demonstrated proven efficacy in various randomized clinical trials[17,18].

Cilostazol is a quinolone derivative that inhibits cellular phosphodiesterase (especially phosphodiesterase 3, PDE3). Many organs, including the heart, contain members of all known PDE isoenzyme families. Since this group of drugs inhibits intracellular phosphodiesterase group enzymes, they increase intracellular cyclic adenosine monophosphate (cAMP) levels. In addition, cilostazol increases the current of L-type calcium channels. With these properties, it has dromotropic

Table 2. Comparison of pre-medication and post-medication electrocardiographic parameters of patients who started cilostazol

ECG parameters	Pre-medication measurements (n= 32)	Post-medication measurements (n= 32)	p
Heart Rate, bpm	68.7 ± 13.6	74.6 ± 11.5	0.067
PR interval, (ms)	156.5 ± 17.1	142.4 ± 20.6	0.418
QRS time, (ms)	87.6 ± 10.3	86.9 ± 8.8	0.601
QT interval, (ms)	389.5 ± 22.7	391.2 ± 31.4	0.345
QTc interval,(ms)	414.34 ± 32.46	430.93 ± 33.25	**0.01**
QTd, (ms)	30.59 ± 19.46	31.87 ± 17.11	**0.01**
Tpe time, (ms)	79.09 ± 18.69	86.81 ± 23.42	**0.01**

Values are expressed as mean ± SD.

and chronotropic effects, which create a predisposition to arrhythmias[19,20]. Various PDE3 inhibitors have also been reported to induce malignant ventricular arrhythmias and increase mortality in patients with congestive heart failure (CHF)[21,22]; however, there is insufficient evidence that cilostazol shows such adverse effects[23]. Although there are studies in the literature suggesting that cilostazol may be a pre-arrhythmogenic drug, there are also publications showing that it may have an anti-arrhythmogenic effect[8,9]. Gamssari et al. documented the development of ventricular tachycardia two days after initiation of cilostazol therapy in a patient with PAD without underlying heart disease[24]. Although cilostazol improved cardiac function in congestive heart failure in an experimental study, increased mortality associated with ventricular arrhythmias was demonstrated in cilostazol-treated control animals[25]. In an experimental study conducted by Barta et al., it was demonstrated that cilostazol might lead to an increase in ventricular arrhythmias and associated mortality[9]. In these experimental studies, it has been suggested that the pre-arrhythmogenic effect of cilostazol use is regulated by intracellular cyclic adenosine monophosphate (cAMP) levels, and this change may be a mechanism that may be involved in mediating electrocardiographic changes[9,26].

It is known to produce a potential proarrhythmic state through prolongation of the QTc interval, increased early post-depolarizations, or exposure of the heart to reentry circuits[27]. Ventricular repolarization times (QT interval) differ between superficial ECG leads. Studies have indicated that a significant difference in repolarization times, specifically QTd (QT dispersion), may elevate the risk of arrhythmias[28]. In experimental studies, the difference in action potential duration between middle myocardial M cells, epicardial and endocardial cells is reflected as transmural dispersion of repolarization (DoR), which is shown as Tpe on the superficial ECG. DoR is an important factor for reentering arrhythmias. Lubinski et al. reported that Tpe correlated with inducible ventricular tachycardia (VT)/ventricular fibrillation (VF)[29]. Watanabe et al. conducted a study demonstrating that electrophysiological studies in patients with prolonged times can induce ventricular tachycardia (VT). In addition, the same team suggested that prolonged Tpe causes spontaneous VT formation in patients[30]. Hence, Tpe has been proposed as a risk marker for ventricular arrhythmias. As a result, the QTc interval, QTd, and Tpe duration are considered electrocardiographic markers that reflect the heterogeneity of ventricular repolarization and are utilized in predicting arrhythmias. In our study, we observed a statistically significant prolongation of QTc interval, QTd, and Tpe durations in patients with peripheral arterial disease (PAD) who had been started on cilostazol treatment for intermittent claudication. While there is no consensus, these findings provide additional support to the hypothesis that cilostazol may have pro-arrhythmogenic effects. Although some earlier studies have suggested that the inhibition of adenosine uptake by cilostazol may counteract the pro-arrhythmic effect of cAMP, thereby mitigating its cardiac side effects[8,23], the results of our study, as well as some previous studies, do not support this hypothesis[9,24,31]. It is understood that various PDE3 inhibitors possess different arrhythmogenic potentials due to their positive inotropic effects, which result in increased intracellular Ca^2+ levels mediated by cAMP[32]. When comparing the arrhythmogenic effects of cilostazol and other PDE3 inhibitors in guinea pig hearts, cilostazol has been shown to have the least positive inotropic and L-type Ca^{2+} flow-increasing effect[33], suggesting that cilostazol is probably less arrhythmogenic than other PDE3s.

Our study had several limitations. Firstly, it was a single-center, retrospective study conducted with a small study population. Secondly, the lack of available data prevented the recording of serial ECG measurements for the subjects. Lastly, the long-term outcomes of the patients were not evaluated in our study. Addressing these limitations would enhance the value of our work.

CONCLUSION

Peripheral artery disease is known to be an independent risk factor for major adverse cardiovascular events such as sudden cardiac death[13]. This raises the concern that the pro-arrhythmogenic effect of cilostazol in PAD patients may have a synergistic effect on MACE. At conventional doses, the clinical benefits of using cilostazol may outweigh the risk of its pro-arrhythmogenic effects in most patients. However, given the fact that peripheral artery disease is often accompanied by a major pro-arrhythmogenic status such as ischemic heart disease, the increased risk of arrhythmias for patients with PAD treated with cilostazol should be kept in mind. Therefore, the use of cilostazol in PAD patients may require close electrocardiographic monitoring, especially if there is accompanying ischemic heart disease.

Ethics Committee Approval: The study was approved by the ethics committee of Kartal Koşuyolu Clinical Research Ethics Committee (Decision no: 28, Date: 19/06/2017) and was performed in accordance with the guidelines of the Declaration of Helsinki.

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - BO, KT; Analysis/Interpretation – BO, KT, Kİ; Data Collection - BO, KT; Writing - BO, KT; Critical Revision - EA, MS, BO, KT; Final Approval- All of authors; Statistical Analysis – KT, Kİ; Overall Responsibility - BO.

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

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Impact of Disulfide/Thiol Redox Couple on Pulse Wave Velocity in Patients with Normal Coronary Angiography

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ABSTRACT

Introduction: The oxidized thiol/disulfide couple has been investigated and reported as a potential risk factor for cardiovascular diseases. Additionally, an increased pulse wave velocity has been identified as a predictor of cardiovascular events.

Patients and Methods: 262 patients were included in our study. Native and total thiol levels, total disulfide levels, disulfide per total thiol ratios, native thiol per total thiol ratios, and disulfide per native thiol level ratios were calculated.

Results: Patients were divided into Pulse Wave Velocity (PWV) low and PWV high groups. Native and total thiol levels were higher in PWV low group compared to PWV high group ($p< 0.001$ for both). The median disulfide value was higher in PWV high group ($p= 0.002$). Disulfide per native thiol and disulfide per total thiol ratio values were higher in PWV high group ($p< 0.001$). Native thiol per total thiol ratios were higher in the PWV-low group ($p< 0.001$).

Conclusion: The disulfide/native thiol pathway may be an indicator for predicting future atherosclerotic cardiovascular events.

Key Words: Antioxidant; thiol

Koroner Anjiyografisi Normal Olan Hastalarda Disülfit/Tiyol Redoks Çiftinin Nabız Dalgası Hızına Etkisi

ÖZET

Giriş: Oksitlenmiş tiyol/disülfit çifti araştırılmış ve kardiyovasküler hastalıklar ve risk faktörleri için potansiyel tehlike olarak rapor edilmiştir. Artan nabız dalga hızının kardiyovasküler olayların habercisi olduğu gösterilmiştir.

Hastalar ve Yöntem: Çalışmamıza 262 hasta dahil edildi. Doğal ve toplam tiyol seviyeleri, toplam disülfit seviyeleri, toplam tiyol başına disülfür oranları, toplam tiyol başına doğal tiyol oranları ve doğal tiyol başına disülfit seviyeleri oranları hesaplanmıştır.

Bulgular: Hastalar *Pulse Wave Velocity* (PWV) düşük ve PWV yüksek gruplarına ayrıldı. Doğal ve toplam tiyol seviyeleri PWV düşük grubunda PWV yüksek grubuna göre daha yüksekti (her iki veri için $p< 0.001$). Disülfit medyan değeri PWV yüksek grupta daha yüksekti ($p= 0.002$). Doğal tiyol başına disülfit ve toplam tiyol başına disülfit oranı değerleri PWV yüksek grupta daha yüksekti ($p< 0.001$). Doğal tiyol/toplam tiyol oranları PWV alt grubunda daha yüksekti ($p< 0.001$).

Sonuç: Disülfit/doğal tiyol yolu, gelecekteki aterosklerotik kardiyovasküler olayları tahmin etmek için bir prediktör olabilir.

Anahtar Kelimeler: Antioksidan; tiyol

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INTRODUCTION

Thiols, a component of cysteine protein that contribute to thiol/disulfide redox couple, are organic composites within the cytosol and mitochondria[1]. Oxidative stress may cause thiols to oxidize and form disulfide bonds, forming a wide range of products. The oxidized products may also be reduced back to the original thiol groups when oxidative stress is removed from the environment. These reduction/oxidation reactions reach equilibrium and homeostasis is achieved[2]. Oxidation reactions occur when this equilibrium is shifted towards the oxidative side due to oxidative stress caused by excessive amounts of reactive oxygen species (ROS)[3]. Increased oxidation and oxidative stress are known to be involved in the pathogenesis of many diseases including hypertension and other cardiovascular diseases[4]. Thiol groups are known to be highly sensitive to oxidation and the formation of thiol-disulfide bonds[4,5]. Thiol-disulfide proteins are actually known to be protective against oxidative damage by direct reaction with ROS and other free radicals as well as enzymatic and non-enzymatic mechanisms[6]. Therefore, the accumulation of thiol-disulfide compounds can be observed in diseases that are associated with oxidative stress. Fibrogenesis, hypertension, and atherosclerosis are often associated with thiol-disulfide accumulation. The accumulation of the oxidized thiol/disulfide couple has been investigated and has been demonstrated as a sign of increased oxidative stress, indicating its potential as a risk factor for cardiovascular diseases[7].

Increased arterial stiffness reflects vascular damage and is a known cardiovascular risk factor[8]. It is considered to be a measure of atherosclerosis severity. Pulse wave velocity (PWV) is an indirect measurement of arterial stiffness and an indicator of subclinical organ damage. Increased pulse wave velocity has been shown to be a predictor of future cardiovascular events[9,10]. In this present study, we aim to investigate a novel oxidative stress marker, thiol/disulfide couple accumulation, and the relationship it may have with PWV in patients with normal coronary arteries shown by coronary angiogram.

PATIENTS and METHODS

Study Population

A total of 262 patients were included in the study, with a mean age of 55.2 ± 11.0 years. The male-to-female ratio was 138 to 125. All patients had undergone coronary angiography within the past six months for various indications, and the results had shown normal coronary arteries. The coronary angiogram was performed diagnostically in response to clinical indications suggestive of ischemic heart disease, such as chest pain, discomfort, and/or abnormal stress test results. The exclusion criteria included the presence of malignancies, other concurrent inflammatory diseases such as infection and autoimmune disorders, diabetes mellitus, familial hypercholesterolemia, major depression, chronic liver and/or renal diseases, recent major surgery, organic CAD, vasospastic angina, heart failure, hypertensive heart disease with left ventricular hypertrophy, severe valvular heart disease, idiopathic hypertrophic or dilated cardiomyopathy. Patients taking antioxidant drugs such as beta-blockers, angiotensin-converting enzyme inhibitors, statins, vitamins, diuretics, and hormone replacement therapy/oral contraceptives were also excluded from the study. Patients who were doing vigorous physical exercise, regular smokers, and alcohol users were also excluded from the study. The study was assessed and approved by the local ethics committee. Written informed consent was obtained from all patients prior to their participation in the study.

Biochemical Parameters

Blood sample collection

Blood samples for biochemical parameters and thiol/disulfide levels were collected from the participants after an overnight fast of eight hours. The samples were obtained from the cubital vein using blood collection tubes. The collected samples were promptly centrifuged for 10 minutes at 3000 rpm to separate the blood serum from other components. The serum was stored at -80 degrees Celsius awaiting analysis. All of the parameters were analyzed from the same serum sample for each patient.

Serum Thiol/Disulfide Homeostasis

Thiol/Disulfide homeostasis tests were conducted using a spectrophotometric assay[11]. A Shimadzu UV-1800 spectrophotometer with a temperature-controlled cuvette holder and a Cobas c501 automated analyzer (Roche) were used for the reduction reaction assay.

The samples were first treated with a reducing agent, sodium borohydride ($NaBH_4$) for a given period to form free functional thiol groups. Any remaining untapped reducing agent $NaBH_4$ residues were consumed and eliminated by adding formaldehyde after the reaction with DTNB [5.5-dithiobis-(2-nitrobenzoic acid)]. This step prevents undesired additional reductions of dynamic disulfide bonds. After these reactions, reduced and native thiol levels were determined spectrophotometrically. Total thiol measurements were obtained using a modified Ellman reagent. The discrepancy between total and native thiol measurements represented the levels of oxidized thiols. Half of this difference corresponded to the amount of dynamic disulfide bonds

present in the samples. Disulfide/total thiol, and native thiol/total thiol ratios were derived from these measurements. Ratios were calculated and recorded as disulfide/native thiol (-S-S)/(-SH), disulfide/total thiol (-S-S-)/(-S-S- + -SH), native thiol/total thiol (-SH)/(-S-S- + -SH).

Echocardiographic examination

All Echocardiographic data were obtained using Vivid-7 (GE Vingmed Sound, Horten, Norway) with a 2.5-3.5 MHz transducer simultaneously with ECG recordings. The echocardiographic examination was conducted by a skilled echocardiographer who was blinded to the patients' clinical and laboratory data. The examination was performed in accordance with the most recent clinical guidelines. The left ventricular ejection fraction (EF) value was calculated using the modified Simpson's technique[12].

Coronary Angiography

Coronary angiography was conducted using Siemens Medical Systems or Toshiba Infinix CC-I monoplane equipment. The procedure utilized 6F diagnostic catheters and followed the standard Judkins technique. Trans-femoral access was selected, with either the right or left femoral artery being used. The procedure was performed by two experienced interventional cardiologists who were blinded to the study, and they obtained images in all standard views and interpreted the results.

Measurement of aortic pulse wave velocity

All recordings were acquired using the ARCSolver method and standard oscillometric blood pressure (BP) measurement procedures[13]. Following a 10-minute rest, a properly sized blood pressure cuff was applied to the right arm of each patient. Applanation tonometry of the radial artery and oscillometric pulse wave recordings at the brachial artery were conducted while the patient was in the supine position. Subsequently, a 10-second pulsed wave analysis recording was obtained with the cuff inflated to the diastolic BP level.

The Mobil-O-Graph NG device was used to obtain the aortic blood pressure curves, aortic systolic blood pressures (SBP), aortic diastolic pressures (DBP), and aortic pulse pressures (PP). Within the time domain, a characteristic point of the aortic blood pressure curve, known as the inflection point, was identified. This inflection point signifies the arrival of the reflected wave in the ascending aorta. The aortic pulse wave velocity (PWV) value was automatically calculated using the Mobil-O-Graph NG software package.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc, Chicago, Illinois, USA). Data are expressed as mean value ± SD. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. A simple T-test was used in the analysis of continuous variables. Categorical variables were analyzed using the Chi-square test. The correlations between PWV, laboratory, oxidative, hemodynamic, and echocardiographic variables were assessed using the Pearson correlation test. A multivariate stepwise linear regression analysis was performed to identify the independent association of PWV. All significant ($p< 0.05$) parameters in the bivariate analysis (Age, SBP, DBP, native thiol, total thiol, disulfide, disulfide/native thiol, disulfide/total thiol, native thiol/total thiol) were selected in the multivariate model. Two-tailed $p< 0.05$ value was considered as statistically significant.

RESULTS

The patients were divided into two subgroups according to their median PWV values. PWV low (mean age 54.2 ± 11.8, n= 129 patients) and PWV high (mean age: 56.3 ± 10.2, n= 133 patients) group. The median PWV value was 7.9 (5.3-12.7). Demographic, and laboratory characteristics, as well as oxidative stress parameters of the patients with PWV low and PWV high groups, are shown in Table 1. The average SBP and DBP values were higher in PWV high group compared with PWV low group ($p= 0.001$ and $p= 0.003$ respectively). Baseline and echocardiographic parameters were not statistically different between the groups ($p> 0.05$ for all mentioned parameters). Triglyceride levels in the PWV high group were higher than in the PWV low group ($p= 0.006$). The other laboratory characteristics were not statistically different between the groups ($p> 0.05$). All oxidative parameters, i.e., native thiol (-SH), total thiol, disulfide, disulfide /native thiol, and native thiol/total thiol were significantly different between groups. Values were higher in PWV low group than in the PWV high group ($p< 0.001$ for both). The median disulfide value was higher in PWV high group than in the PWV low group ($p= 0.002$). The disulfide/native thiol ratio and disulfide/total thiol ratios were higher in PWV high group ($p< 0.001$). Native thiol/total thiol ratio's median values were higher in the PWV low group ($p< 0.001$). Regression analyzes between PWV (m/s) and Total Thiol (μmol/L) ($r=-0.445$, $p< 0.001$) and between PWV (m/s) and Disulphide/Native Thiol ($r= 0.532$, $p< 0.001$) were shown in Figure 1 and Figure 2, respectively.

Bivariate and multivariate relationships of PWV

Pulse wave velocity was significantly associated with age, SBP, DBP, native thiol, total thiol, disulfide, disulfide/native thiol, and disulfide/total thiol (Table 2).

Table 1. Clinical, laboratory, and oxidative parameters

Variables	PWV_{low} group* (n= 129)	PWV_{high} group* (n= 133)	p
Baseline characters			
Age (years)	54.2 ± 11.8	56.3 ± 10.2	0.130
Gender (male)	64 (49.2%)	62 (45.6%)	0.319
BMI (kg/m^2)	28.9 ± 5.4	28.8 ± 4.4	0.898
Heart rate (b/m)	73.5 ± 10.5	73.3 ± 10.3	0.895
SBP (mmHg)	117.1 ± 7.4	120.4 ± 8.4	**0.001**
DBP (mmHg)	73.2 ± 7.5	75.8 ± 6.4	**0.003**
Laboratory Findings			
Glucose (mg/dL)	90.7 ± 11.0	89.9 ± 15.7	0.657
Hemoglobin (g/dL)	13.5 ± 1.6	13.2 ± 1.5	0.082
WBC ($10^3/\mu L$)	7.2 ± 2.0	7.7 ± 2.3	0.063
TC (mg/dL)	182.1 ± 41.9	190.9 ± 41.1	0.118
Triglyceride (mg/dL)	145.6 ± 75.8	176.1 ± 86.5	**0.006**
HDL (mg/dL)	41.9 ± 12.5	40.0 ± 10.5	0.216
LDL (mg/dL)	121.7 ± 37.8	125.5 ± 35.0	0.448
Creatinine (mg/dL)	0.74 ± 0.2	0.76 ± 0.2	0.693
Oxidative parameters			
Native thiol (µmol/L)	269.2 ± 51.1	217.1 ± 58.8	**<0.001**
Total thiol (µmol/L)	299.6 ± 55.3	251.3 ± 61.6	**<0.001**
Disulphide (µmol/L)	14.7 ± 6.7	17.4 ± 7.4	**0.002**
Disulphide/Native thiol	0.06 ± 0.03	0.09 ± 0.08	**<0.001**
Disulphide/Total thiol	0.05 ± 0.02	0.07 ± 0.04	**<0.001**
Native thiol/Total thiol	0.90 ± 0.04	0.85 ± 0.08	**<0.001**

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, WBC: White blood cell, TC: Total cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, b/m: Beat/minute, PWV: Pulse wave velocity.
*Subjects were grouped according to their median (min-max) PWV value as ''7.9 (5.3-12.7)"

Table 2. Multivariate linear regression analysis for oxidative parameters

	Pearson correlation		Standardization	
Variables	coefficients	p	B-regression coefficients	p
Age	0.157	**0.011***	-0.007	0.899
SBP (mmHg)	0.161	**0.008***	0.102	0.099
DBP (mmHg)	0.168	**0.006***	0.090	0.141
Native thiol (µmol/L)	-0.511	**<0.001***	-	
Total thiol (µmol/L)	-0.445	**<0.001***	-0.309	**<0.001**
Disulphide (µmol/L)	0.310	**<0.001***	-	
Disulphide/Native thiol	0.532	**<0.001***	0.348	**<0.001**
Disulphide/Total thiol	0.539	**<0.001***	-	
Native thiol/Total thiol	-0.460	**<0.001***	-	

SBP: Systolic blood pressure, DBP: Diastolic blood pressure.
*Variables with a p-value of <0.05 were included in the multivariable regression analysis.

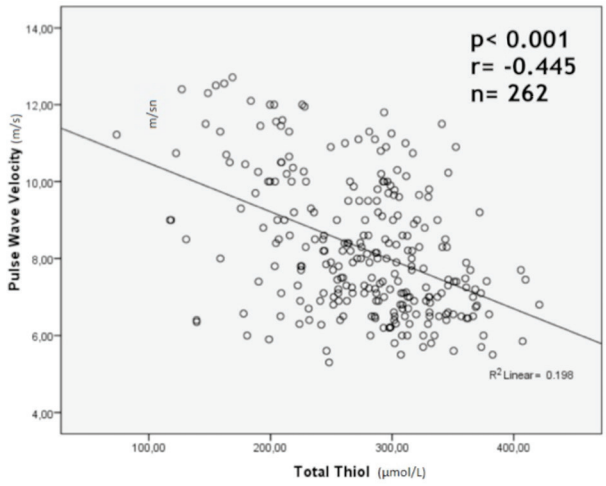

Figure 1. Regression analysis between Pulse wave Velocity (m/s) and Total Thiol (µmol/L).

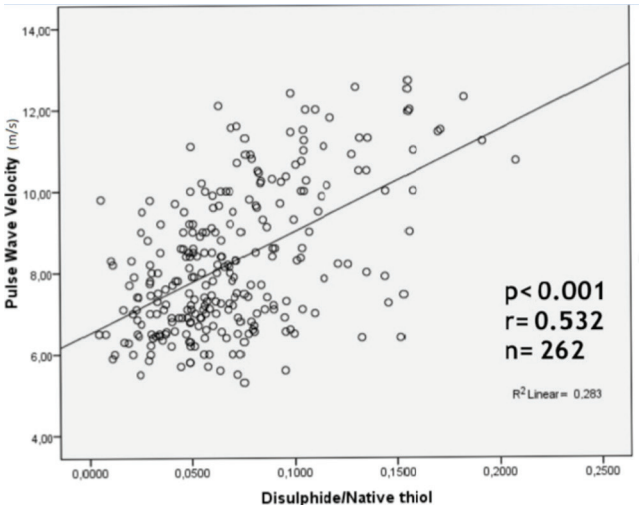

Figure 2. Regression analysis between Pulse Wave Velocity (m/s) and Disulphide/Native Thiol.

DISCUSSION

In the present study, we demonstrated a significant correlation between arterial stiffness assessed by PWV and oxidative stress parameters such as thiol/disulfide redox couple in patients with normal coronary arteries. Our results show that impairment in PWV is associated with an increase in disulfide levels and a decrease in thiol levels which reflects impaired oxidative and anti-oxidation pathways.

Tissue damage and corrupted oxidation mechanisms lead to endothelial dysfunction, apoptosis, and atherosclerosis[14]. Various oxidative-modified agents have been investigated to show oxidative stress and coronary atherosclerosis[15]. Thiol/disulfide redox couple is one of them, and a rapidly growing research area. A decrease in (-SH)/(-S-S-) has been shown to be a predictor of apoptosis, which may lead to accelerated atherosclerosis via macrophages[16-18]. Thiols are organosulfur compounds containing sulfhydryl components. Noxious reactive oxygen species can influence sulfhydryl components along with thiol groups. Thiols can react with one or two electron oxidants, yielding sulfenic acids. Sulfenic acids are bruise products that tend to link with another thiol and formed to oxidized disulfide. This leads to oxidation of thiol molecules and disulfide products are formed. This pathway is reversible, and oxidation can be reversed[1,11]. Loss of equilibrium in reactive oxygen species and abnormal thiol/disulfide ratio is associated with deterioration in intracellular signaling and regulation, and protein function. This in turn leads to accelerated cell death and promotes to atherosclerosis[5,19].

In several experimental laboratory studies, It has been shown that the alterations of the (-S-S)/(-SH) ratio may occur in conjunction with age, diabetes mellitus as well as atherosclerosis, and reported oxidation via chemical agents may lead to increase in apoptosis and vascular aging[16,17]. Oxidative stress, thiol oxidation, and elevated disulfide levels have been shown as critical factors in progress for various diseases such as type 1 diabetes mellitus, cancer, and hypertension[20-22]. All of the aforementioned studies concluded that the thiol/disulfide redox couple may be a fundamental protective guard against oxidative stress and disease progression. Another common finding of these studies was decreased thiol, thiol/disulfide ratio and increased disulfide levels occurred as a result of oxidative damage. A recent study demonstrated an association between the thiol/disulfide ratio and syntax score in patients who had a myocardial infarction[5]. They reported a positive correlation between increased disulfide molecules and coronary artery disease severity. Similarly, decreased median thiol/disulfide ratio was an independent predictor for myocardial infarction in multivariate analysis. In another study, authors examined acute patients with acute myocardial infarction and healthy populations according to their demographical and clinical characteristics. Alongside expected results (troponin, high-density lipoprotein cholesterol), native thiol (-SH), total thiol (-S-S- + -SH), disulfide/native thiol ratio (-S-S-)/(-SH), disulfide/total thiol ratio (-S-S-)/(-S-S- + -SH) levels were significantly different between the groups[23]. Their results support previous reports, and the effect of shifted thiol/disulfide balance on acute cardiovascular events.

PWV is a diagnostic marker of arterial stiffness, and it has been used to stratify risk for subclinical organ damage[10]. Basic mechanisms of arterial stiffness and increased PWV are the ultimate results of inappropriate architectural components of arterial vessels. The process of arterial stiffness, characterized

by increased intraluminal pressure, reduced elastin quality, increased collagen accumulation, vascular muscle thickening, and excessive fibrogenesis, can be triggered by factors such as advancing age, hypertension, and external stimuli. These factors contribute to the unfavorable manifestations of arterial stiffness. These changes occur as PWV increases[24,25]. Recently, PWV has been shown to be a decisive parameter as an independent predictor of future cardiovascular events in patients with acute myocardial infarction[9]. Blacher et al. concluded that PWV is more specific as an independent predictor of cardiovascular events compared to conventional cardiovascular risk factors[26]. In another study, patients with no prior cardiovascular events or symptoms were studied for six years via measuring PWV; the authors reported that patients who did have a cardiovascular event in this period had higher PWV compared to the event-free group[27]. Pulse wave velocity has a positive correlation with oxidative stress markers in patients without cardiovascular disorders[28]. Since increased PWV may be observed even in patients without cardiovascular events, dissemination of arterial stiffness should be evaluated in high-risk populations[25]. Patel et al. observed positive correlations between oxidized thiols and arterial stiffness markers in healthy subjects. Oxidized thiols such as cystine had an independent correlation with PWV in univariate and multivariate models[29]. Despite these findings, Sharmen et al. reported applying a thiol component called alpha-lipoic acid in healthy subjects, neither oral nor intravenous forms, did not influence PWV and oxidative stress parameters[30].

In our study, PWV values had a positive correlation with disulfide, disulfide/native thiol ratio, and disulfide/total thiol ratio. Pulse wave velocities had a negative correlation with native thiol and native thiol/total thiol ratio. Besides a known prognostic indicator in acute coronary heart syndromes, oxidative thiol, and increased disulfide may show oxidative stress and elevated inflammation in patients without coronary artery disease. Based on our findings, we recommend conducting further investigations in populations with a high suspicion of coronary artery disease before disease progression occurs. If necessary, primary treatment should be initiated based on these investigations.

The absence of a follow-up period is one of the limitations of our study. Another limitation is the relatively small sample size of our population. Moreover, although the patients had similar dietary and exercise habits, there was a lack of precise follow-up regarding these parameters. Lastly, it should be noted that the diagnosis of a normal coronary angiogram may be subjective since intravascular ultrasound (IVUS) was not utilized in the evaluation of patients.

CONCLUSION

Increased oxidative stress via the disulfide/native thiol (-S-S-)/(-SH) pathway may be an indicator for predicting future atherosclerotic cardiovascular events. To enhance our understanding of the mechanisms underlying vascular aging, it is crucial to conduct additional studies that assess changes in oxidative stress, thiol-disulfide accumulation, and their impact on arterial stiffness.

Ethics Committee Approval: The approval for this study was obtained from Adana Numune Training and Research Hospital Non-invasive Clinical Research Ethics Committee (Decision no: 79, Date: 24.12.2014).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - SA; Analysis/Interpretation - MG, HÇ; Data Collection - SA, HH, ÖE; Writing - SA, HH; Critical Revision - HH, MG; Final Approval - All of authors; Statistical Analysis -MG; Overall Responsibility - SA.

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

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Preoperative Atrial Fibrillation and Coronary Artery Bypass Grafting Outcomes

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ABSTRACT

Introduction: Traditionally, atrial fibrillation is considered a comorbid factor for coronary artery bypass surgery as well as other surgeries, however, current literature is still limited. In this study, the effects of preoperative atrial fibrillation on coronary artery bypass grafting were investigated.

Patients and Methods: Following the hospital's clinical trials ethics committee approval, data from 151 patients who underwent isolated coronary artery bypass surgery were collected with the assistance of the hospital's electronic records system. The follow-up duration was 12 months. Statistically significant P value cut-off taken as 0.05.

Results: The mean age was 61.5 and 26.6% (n= 40) of the patients were female. Preoperative atrial fibrillation (Afib) prevalence was 13.3% (n= 20). No significant differences were observed in patient demographics, metabolic, systemic, and cardiovascular conditions between the group with preoperative atrial fibrillation and the control group (p> 0.05). However, the previous myocardial infarction rate was found higher (38.9 vs. 70.0, p= 0.009), and carotid artery stenosis disease prevalence was found lower (18.2 vs. 0.0, p= 0.038), also mean glomerular filtration rate (GFR) was found lower (85.9 vs. 69.7, p= 0.002) in the patients with Afib. Intraoperative parameters were not statistically different among the group (p> 0.05). Despite the preoperative dysthymia history, myocardial infarction prevalence, and poor kidney function; there was no difference in terms of postoperative acute kidney injury rates, stroke rates, perioperative complication rates, and thirty-day and 12-month survival (p> 0.05). However, the re-revascularization requirement was higher in patients in the Afib group.

Conclusion: Atrial fibrillation is a prevalent comorbidity in coronary artery bypass grafting patients. However, it was not found as a factor that related to mortality or morbidity and coronary surgery seems feasible in this patient group.

Key Words: Atrial fibrillation; coronary artery bypass; ischemic heart disease

Preoperatif Mevcut Atriyal Fibrilasyon ve Koroner Arter Bypass Greftleme Sonuçları

ÖZET

Giriş: Geleneksel olarak atriyal fibrilasyon, koroner arter baypas cerrahisi ve diğer kardiyak cerrahiler için komorbid bir faktör olarak kabul edilir, ancak mevcut literatür hala sınırlıdır. Bu çalışmada, koroner arter baypas greftlemesinde ameliyat öncesi var olan atriyal fibrilasyonun etkileri araştırılmıştır.

Hastalar ve Yöntem: Hastane klinik araştırmaları etik kurul onayı alındıktan sonra hastane elektronik kayıt sistemi yardımıyla izole koroner arter baypas ameliyatı yapılan 151 hastanın verileri toplandı. Takip süresi 12 aydı. İstatistiksel olarak anlamlı P değeri kesim değeri 0.05 olarak belirlendi.

Bulgular: Çalışma kohortunun yaş ortalaması 61,5 bulundu ve hastaların toplamda %26.6'sı (n= 40) kadındı. Ameliyat öncesi var olan atriyal fibrilasyon (Afib) prevalansı %13.3 (n= 20) bulundu. Ameliyat öncesi atriyal fibrilasyonu olan hastalar ile kontrol grubu arasında hasta demografik özellikleri, metabolik, sistemik ve kardiyovasküler komorbiditeler açısından fark bulunmadı (p> 0.05). Ancak geçirilmiş miyokard enfarktüsü oranı daha yüksek (38.9'a karşı 70.0, p= 0.009) ve karotis arter stenoz hastalığı prevalansı daha düşük bulundu (18.2'ye karşı 0.0, p= 0.038), ayrıca Afib'li hastalarda GFR (glomerular filtration rate) daha düşük bulundu (85.9'a karşı 69.7, p= 0.002). İntraoperatif parametreler grup arasında istatistiksel olarak farklı değildi (p> 0.05). Preoperatif distimi öyküsü, miyokard enfarktüsü prevalansı ve zayıf böbrek fonksiyonlarına rağmen, postoperatif akut böbrek hasarı oranları, inme oranları, perioperatif komplikasyon oranları ve otuz günlük ve 12 aylık sağkalım açısından fark yoktu (p> 0.05). Ancak Afib grubu olan hastalarda revaskülarizasyon gereksinimi daha yüksekti.

Sonuç: Atriyal fibrilasyon, koroner arter baypas greftleme hastalarında yaygın bir komorbiditedir. Ancak bu hasta grubunda mortalite veya morbidite ile ilişkili bir faktör olarak bulunmamıştır ve koroner cerrahi bu hastalar için uygulanabilir görünmektedir. Çalışmamızın sonuçlarının daha büyük vaka serili çok merkezli çalışmalar ile doğrulanması elzemdir.

Anahtar Kelimeler: Atriyal fibrilasyon; koroner arter bypass; iskemik kalp hastalığı

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INTRODUCTION

Atrial fibrillation (Afib) is the most common form of dysrhythmia, affecting more than five million patients in the United States alone[1]. The frequency of Afib is quite high in patients with ischemic heart disease as a result of the disruption of the electrical conduction system of the heart due to injury due to myocardial ischemia[1].

The incidence of atrial fibrillation (Afib) in patients undergoing coronary surgery ranges from 6.1% to 15.8%, with an average of 10%. The impact of this common preoperative condition on postoperative outcomes is still a subject of debate. According to Khiabani et al., preoperative Afib is associated with an increased risk of all-cause morbidity and mortality in patients undergoing coronary artery bypass grafting (CABG). In addition, Malaisrie et al. found that patients with preoperative Afib have higher rates of reoperation, permanent stroke, prolonged ventilation, new renal failure, deep sternal wound infection, and in-hospital death. With the advent of the percutaneous era, determining the prevalence and potential effects of this comorbidity in coronary surgery is gaining importance[2-5].

In this study, the feasibility of coronary surgery for patients with preoperative Afib was evaluated. The primary outcome was in-patient outcomes, and the secondary outcome was coronary surgery outcomes such as repeat revascularization rate and overall survival.

PATIENTS and METHODS

Study Design

151 patients who underwent coronary bypass grafting surgery for ischemic heart disease were included in this study. This study has aimed to investigate preoperative Afib effects on coronary artery bypass grafting surgery results.

Ethical Approval

Our institute's ethical committee approved the study, which was conducted according to the ethical standards of the responsible committee on human experimentation (both institutional and national) as well as the Helsinki Declaration of 1975, revised in 2000 by the World Medical Association.

Data Collecting and Follow-up

Based on ethical approval, the primary surgeon who applied the treatment made the data collection. Demographic and medical features such as age, gender, body mass index, hypertension, carotid artery disease, previous myocardial infarction, additional structural heart disease, left ventricular ejection fraction, diabetes mellitus, chronic obstructive pulmonary disease, malignancy, obesity, preoperative hemoglobin, serum creatinine, preoperative glomerular filtration rate, and preoperative hematocrit were taken as preoperative features. Intraoperative death, sternal dehiscence, one-year revascularization requirement, acute kidney injury, cardiopulmonary resuscitation, perioperative complications including bleeding, stroke, thirty-day mortality, postoperative hematocrit, duration of intensive care (days) and hospital stay (days) were taken as postoperative outcomes. Intraoperative data such as the number of distal anastomoses, cardiopulmonary bypass time (minute), and aortic cross-clamp time (minute) were compiled from intraoperative notes by the assistant surgeon. The 12-month postoperative status was examined for follow-up by checking the national database.

Statistical Analysis

Categorical variables were reported as a proportion and were analyzed using χ^2 or Fisher exact tests, as appropriate. Continuous variables were reported as mean and were compared using student t-tests between the two groups. In addition, the log-rank Kaplan-Meier test was used for calculating the differences in 12-month survival among the groups.

RESULTS

Preoperative Status and Demographics

The study cohort's median age was 61.5 and 26.6% (n= 40) of the patients were female. The preoperative Afib was seen in 20 patients which makes up to 13.3% of all of our patients. There was no difference in demographics such as age (61.5 vs. 61.5, p= 0.582), gender distribution (27.3% vs. 20.0%, p= 0.491), and body mass index (29.0 vs. 28.6, p= 0.473) among the groups. Carotid artery disease prevalence (18.2% vs. 0.0%, p= 0.038) was statistically significantly higher in the control group however on the other hand previous myocardial infraction prevalence (38.9% vs. 70.0%, p= 0.009) was found significantly higher in the patients with the Afib group. The Afib group has worse renal functions than the control group (p= 0.002). The rest of the preoperative parameters such as additional structural heart disease, left ventricular ejection fraction, diabetes mellitus, chronic obstructive pulmonary disease, malignancy, obesity, preoperative hemoglobin, serum creatinine, and hematocrit were not found to be statistically different (p> 0.05).

Perioperative results

The mean number of distal anastomoses for the groups was 2.9 and 3.2. cardiopulmonary bypass time was 86.6 minutes and 85.3 minutes. Aortic cross-clamp time was found to be 51.9 minutes and 49.8 minutes. There was no significant difference between the control group and the Afib group in terms of intraoperative parameters (Table 2).

Table 1. Preoperative medical history

Variables	Control Group	Patients with Atrial Fibrillation	p
Age (mean)	61.5	61.5	0.582
Gender (female %)	27.3	20.0	0.491
Body Mass Index (mean)	29.0	28.6	0.473
Hypertension (yes, %)	50.8	45.0	0.631
Carotid Artery Disease (yes, %)	**18.2**	**0.0**	**0.038**
Previous Myocardial Infarction (yes, %)	**38.9**	**70.0**	**0.009**
Additional Structural Heart Disease (yes, %)	7.6	0.0	0.201
Left ventricular ejection fraction (% mean)	57.3	49.9	0.128
Diabetes mellitus (yes, %)	46.2	40.0	0.603
Chronic Obstructive Pulmonary Disease (yes, %)	22.7	30.0	0.476
Malignancy (yes, %)	3.1	5.0	0.650
Obesity (yes, %)	32.8	45.0	0.286
Preoperative Hb (g/dL)	13.5	14.4	0.823
Creatinine (mg)	0.98	0.97	0.422
Preoperative GFR (mL/min)	**85.9**	**69.7**	**0.002**
Preoperative Haematocrit (%)	40.3	42.5	0.751

GFR: Glomerular filtration rate.

Table 2. Intraoperative results

Variables	Control Group	Patients with Atrial Fibrillation	p
Number of distal anastomoses (n)	2.9	3.2	0.130
Cardiopulmonary bypass time (minute)	86.6	85.3	0.763
Aortic cross-clamp time (minute)	51.9	49.8	0.762

Intraoperative death has never been observed; however, 30-day mortality was 2.3% in the control group, even though it was not seen in the Afib group. Despite the low mean GFR in the Afib group, there was no significant difference between the control and the Afib groups in terms of acute kidney injury frequency. Regarding perioperative complications (perioperative complications general, sternal dehiscence, cardiopulmonary resuscitation requirement), no significant distinction between the groups was found, and recovery parameters such as intubation duration, length of intensive care unit (ICU) stay, and length of hospital stay. Interestingly, there was no significant difference between the two groups in terms of stroke in the postoperative period (Table 3).

Coronary Artery Bypass Grafting Outcomes

In this study, coronary artery bypass grafting outcomes were taken as 12-month repeat revascularization and 12-month overall survival. Repeat revascularization requirement was seen in one patient (0.7% overall), it was in the Afib group (0.0% vs 5.0%, p= 0.010). The overall survival rate was found to be 95.4% overall, which was 100.0% and 94.7% in the Afib group and control group respectively (p= 0.273).

DISCUSSION

Our study found a preoperative Afib prevalence of 13.3% in our cohort of patients undergoing coronary artery bypass grafting. A systematic review and meta-analysis conducted by Saxena et al. found a pooled prevalence of Afib in patients undergoing cardiac surgery of 5.1% (n= 19,706), with significant heterogeneity among the 12 studies (n= 389,998)[6]. In other studies, the incidence of Afib in patients undergoing coronary surgery typically falls within the range of 6.1% to 18.6%, with an average of approximately 10%[2-5]. Therefore, our results support the notion that Afib is a common comorbidity in patients undergoing CABG and highlights the need for clinicians to be aware of its presence when evaluating these patients.

Table 3. Postoperative outcomes

Variables	Control Group	Patients with Atrial Fibrillation	p	Odds Ratio
Intraoperative death (yes, %)	0.0	0.0	-	-
Sternal dehiscence (yes, %)	6.2	0.0	0.254	0.94
One-year revascularization requirement (yes, %)	**0.0**	**5.0**	**0.010**	**1.05**
Acute kidney injury (yes, %)	6.1	5.0	0.851	0.82
Cardiopulmonary resuscitation (in-hospital) (yes, %)	2.3	5.0	0.478	2.3
Perioperative complications including bleeding (yes, %)	6.1	5.0	0.851	0.82
Stroke (yes, %)	5.3	5.0	0.949	0.93
Thirty-day mortality (yes, %)	2.3	0.0	0.496	0.98
Postoperative Hct (%)	**29.0**	**30.4**	**0.000**	-
ICU duration (Days)	5.2	3.9	0.274	-
Length of stay inc. ICU duration (Days)	9.9	8.6	0.373	-

ICU: Intensive care unit.

In our study, the patients of both the preoperative Afib group and the control group had similar demographic, metabolic, systemic, and cardiovascular conditions. However, there were certain differences observed between the two groups. The incidence of previous myocardial infarction was higher in the preoperative Afib group, while the prevalence of carotid artery stenosis disease and mean GFR were lower. According to the study conducted by Malaisrie et al. patients with preoperative Afib who underwent CABG were found to be older and had a higher prevalence of comorbidities such as hypertension, renal failure, chronic lung disease, lower ejection fraction, and heart failure[3]. Furthermore, the study by Ad et al. reported that patients with preoperative Afib undergoing CABG were older and had a higher prevalence of diabetes mellitus, hypertension, and congestive heart failure[7]. According to the review by Khiabani et al., preoperative Afib is associated with a higher risk of perioperative complications and mortality[4]. Also, a recent meta-analysis carried out by Saxene et al. discussed that preoperative Afib is identified as an independent risk factor for adverse perioperative outcomes and decreased overall survival following CABG[6]. In contrast, no significant differences were found between the groups in terms of perioperative complications, such as sternal dehiscence, cardiopulmonary resuscitation requirement, and general complications in our study. Additionally, no significant differences were observed in the incidence of 30-day and 12-month survival between the groups.

Notably, our study demonstrated the absence of a significant difference in the incidence of postoperative stroke between the two groups. It is worth noting that previous studies have shown conflicting results regarding the association between preoperative Afib and postoperative stroke. Our finding is consistent with the results of some previous studies that did not report a noticeable rise in the occurrence of postoperative stroke among patients with Afib[3,8,9]. On the other hand, some previous studies showed that preoperative Afib is associated with an elevated risk of perioperative stroke[6,10]. In our study, the need for re-revascularization was found to be higher in the preoperative AF group. Despite the limited sample size, this finding is consistent with some previous studies that have reported higher rates of repeat revascularization in patients with preoperative Afib[11]. These findings highlight the need for careful follow-up and monitoring of patients with preoperative Afib who undergo coronary artery bypass grafting surgery. To achieve improved outcomes in these patients, current literature is discussing various points such as concomitantly arrhythmia surgery in severe cases or prophylactic medications preoperatively for arrhythmia, postoperatively for thromboembolic events[12,13]. In our institutional experience, we did not implement any additional or different medication protocols specifically for patients with preoperative atrial fibrillation. However, we have been implementing an enhanced recovery after surgery (ERAS) protocol for patients undergoing coronary artery bypass grafting (CABG), which includes practices such as early mobilization of patients. ERAS protocol might improve the outcomes in terms of length of stay and related complications[14].

Limitations of the study include its retrospective design, relatively small sample size, and short follow-up duration of 12 months. Additionally, the study only included patients undergoing isolated coronary artery bypass grafting surgery, so the findings may not be generalizable to other cardiac surgeries.

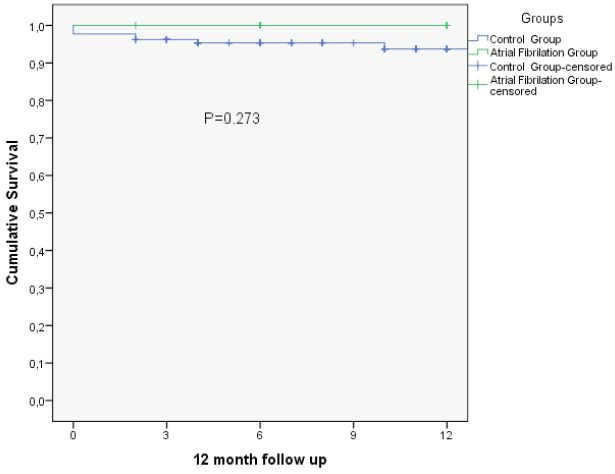

Figure 1. 12-month overall survival graph.

Future studies with larger sample sizes, longer follow-up durations, and more diverse patient populations may help to further explain the impact of preoperative Afib on CABG outcomes.

CONCLUSION

In conclusion, our study indicates that coronary artery bypass grafting surgery is a viable option for patients with preoperative atrial fibrillation. However, it is crucial to emphasize the importance of diligent follow-up and monitoring of these patients, particularly regarding the potential need for repeat revascularization.

Ethics Committee Approval: The approval for this study was obtained from Eskişehir City Hospital Non-invasive Clinical Research Ethics Committee (Decision no: ESH/GOEK 2023/2, Date: 15.03.2023).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

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

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Treatment of Deep Mediastinal Infections Following Cardiac Surgery with Pectoral Muscle Flap

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ABSTRACT

Introduction: Mediastinitis is a rare occurrence following cardiac surgeries; however, it is a significant cause of both mortality and morbidity. Given the significance of mediastinal infections, early diagnosis, and treatment become of paramount importance. The management of this condition necessitates a multidisciplinary approach, involving collaboration and coordination among various medical specialties.

Patients and Methods: 21 patients with a diagnosis of deep mediastinal infection who were treated at Eskişehir Osmangazi University Medical Faculty Hospital between January 2015 and May 2021 were included in the study. Broad-spectrum antibiotic therapy, serial debridement, and vacuum-assisted closure were applied to all patients. Among the patients who exhibited negative blood cultures and developed granulation tissue, those with tissue losses that did not extend to the sternum incision sites were assessed for potential flap procedures in conjunction with plastic and reconstructive surgery. In such cases, closure of the wound was achieved using a pectoral muscle flap. All patients were followed for one year.

Results: Among the patients, 14 (66.6%) were female and seven (33.3%) were male, with a mean age of 62.7 ± 6.5 (range: 41-76 years). Three of the 21 patients included in the study had type I, two had type II, and 16 had type IIIA mediastinitis. *Staphylococcus aureus* (*S. aureus*) was the most commonly isolated microorganism with 11 patients (52.3%). The right pectoralis major muscle was used in four patients (19%), the left pectoralis major muscle in four patients (19%), and the bilateral pectoralis major muscle in 13 patients (62%). There was no need for re-intervention in the follow-up of the patients. No mortality because of infection, surgical muscle flap closure, and/or cardiac causes was observed in any of the patients who were treated.

Conclusion: Mediastinitis is a costly treatment, requiring prolonged hospitalization and carrying the risk of mortality. The main objective is to prevent the occurrence of mediastinitis. We believe that this objective should be pursued through a multidisciplinary approach involving cardiovascular surgery, infectious diseases, and plastic and reconstructive surgery units.

Key Words: Mediastinitis; debridement; pectoralis flap

Kalp Cerrahisi Sonrası Görülen Derin Mediastinal Enfeksiyonların Pektoral Kas Flebi ile Tedavisi

ÖZET

Giriş: Mediastinit, kalp cerrahisi sonrası nadir görülmesine rağmen ciddi bir mortalite ve morbidite sebebidir. Bu nedenle derin mediastinal enfeksiyonların erken tanı ve tedavisi çok önemlidir. Bu durumun yönetimi ise multidisipliner yaklaşım gerektiren bir süreçtir.

Hastalar ve Yöntem: Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Hastanesinde Ocak 2015-Mayıs 2021 tarihleri arasında görülen 21 derin mediastinal enfeksiyon tanılı hasta çalışmaya dahil edildi. Hastaların tamamına geniş spektrumlu antibiyoterapi, seri debridman ve vakum yardımlı kapama sistemi tedavileri uygulandı. Kültür sonucu negatifleşen ve yara yerinde granülasyon dokusu gelişen hastalardan sternum insizyon yerlerinde doku kaybı olan hastalara pektoral kas flebi ile yara yeri kapama yapıldı. Tüm hastalar bir yıl boyunca takip edildi.

Bulgular: Hastaların 14'ü kadın (%66.6), yedisi erkek (%33.3) olup yaş ortalamaları 62.7 ± 6.5 (dağılım: 41-76 yaş) idi. Çalışmaya dahil olan 21 hastanın üçü tip I, ikisi tip II, 16'sı ise tip IIIA mediastinit olgularıydı. En çok izole edilen mikroorganizma 11 hastada görülen *Staphylococcus aureus*tu (*S. aureus*). Dört hastada (%19) sağ pektoralis majör kası, dört hastada (%19) sol pektoralis majör kası, 13 hastada (%62) ise bilateral pektoralis majör kası flep olarak kullanıldı. Hastaların takiplerinde tekrar girişim ihtiyaçları olmadı. Tedaviye alınan hiçbir hastada enfeksiyon nedenli, cerrahi kas flebi ile kapamaya bağlı ve/veya kardiyak nedenlere bağlı mortalite gözlenmedi.

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Sonuç: Derin mediastinal enfeksiyonların tedavisi yüksek maliyetli, uzun süreli yatış gerektiren ve ölüm ile sonuçlanabilen bir durumdur. Öncelikli amaç kalp cerrahisi sonrasında mediastinit gelişmesine engel olmaktır. Mediastinit gelişen hastalarda kalp damar cerrahisi, enfeksiyon hastalıkları ve plastik ve rekonstrüktif cerrahi hekimlerinin multidisipliner yaklaşımı ile tedavi sürecini yönetmenin daha olumlu sonuçlar sağlayacağını düşünmekteyiz.

Anahtar Kelimeler: Mediastinit; debritman; pektoral flep

INTRODUCTION

Sternal wound infections are rarely observed following cardiac surgeries, yet they continue to be serious complications increasing mortality and morbidity and causing high hospitalization costs[1-3]. Given the significance of mediastinal infections, early diagnosis, and treatment become of paramount importance. When sternal wound infections are limited to the skin and subcutaneous tissue, they are categorized as superficial wound infections. However, if the infection progresses to affect the muscle, fascia, sternum, and mediastinum, they are classified as deep wound infections[4]. Despite efforts in developing antibiotics and implementing preoperative and postoperative care protocols to mitigate the risk of such infections, it is important to note that complete prevention of these infections is currently not possible. Following cardiac surgery, the probability of developing mediastinitis varies between 0.4% and 5%[5]. Mediastinitis is influenced by numerous risk factors, which can be categorized into preoperative, intraoperative, and postoperative factors. Preoperative risk factors include conditions such as diabetes mellitus (DM), congestive heart failure, advanced age, smoking, low Ejection Fraction (EF), kidney failure, and obesity[6-9]. Intraoperative risk factors encompass various factors including emergency surgeries, prolonged surgical procedures, compromised sternum structure, inadequate sternotomy techniques, excessive use of electrocautery and bone wax, and the utilization of the internal mammary artery[6-9]. Reoperations, incompatibility of patients and deficiencies in personal care, need for repetitive blood transfusion, and prolonged mechanical ventilation support are some of the risk factors in the postoperative period[7-12].

The initial step involves the identification and isolation of the causative agent, followed by the administration of appropriate antibiotic therapy. The process requires a multidisciplinary approach including antibiotics, debridements, and postoperative follow-up in cardiac surgery. Subsequent steps in the standard treatment of mediastinitis may involve serial debridements, mediastinal irrigation, negative-pressure wound therapy, and partial sternum removal. In cases where standard treatments prove ineffective, closure techniques utilizing muscle flaps are employed. The advancement of these methods has substantially reduced morbidity and mortality associated with mediastinitis[13].

The purpose of the present study was to investigate the impact of the muscle flap closure method on the reduction of morbidity and mortality associated with deep mediastinal infections following cardiac surgery. These infections are known to pose significant risks in terms of morbidity and mortality.

PATIENTS and METHODS

The approval of the Eskişehir Osmangazi University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee was obtained for the study (Approval Date: 26.07.2022, and Approval Number: E-25403353-050.99-364120). The data of 982 patients who underwent cardiac surgery with sternotomy by the same surgical team at Eskişehir Osmangazi University Medical Faculty Hospital between January 2015 and May 2021 were analyzed retrospectively. During this study period, a total of 36 patients with a preliminary diagnosis of deep mediastinal infection were treated at our clinic. Patients who exhibited discharge at the sternum incision site but showed no growth in culture, patients whose initial antibiotic therapy was modified due to allergic reactions, patients with superficial infections, and patients who could undergo primary closure after using a vacuum-assisted closure system due to minimal tissue loss were excluded from the study. After exclusion, 21 patients were found eligible for the study and classified according to the Mediastinitis Classification made by El Oakley and Wright (Table 1)[5]. Greig et al., on the other hand, classified sternum infections according to their localizations and stated the grafts suitable for use according to this classification (Table 2)[14].

After the cultures were taken from the wounds and the discharges of the patients at the sternum incision, broad-spectrum antibiotic therapy was started (Vancomycin + Meropenem) in all patients with the recommendation of the infectious diseases unit. The antibiotic treatment for patients with determined culture results was arranged based on the antibiograms. Tigecycline + Meropenem treatment was initiated for two patients. Acute phase reactants and kidney and liver function tests were closely monitored during the medical treatment of the patients. The patients underwent serial debridements under the supervision of the plastic and reconstructive surgery clinic. The sternum incisions were fully opened (Figure 1), and debridement was performed on the

Table 1. The mediastinitis classification of El Oakley and Wright

Types	Characteristics
Type I	Mediastinitis occurring in the first postoperative two weeks without a risk factor
Type II	Mediastinitis occurring within postoperative 2-6 weeks without risk factors
Type IIIA	Type I Mediastinitis with one or more risk factors
Type IIIB	Type II Mediastinitis with one or more risk factors
Type IVA	Type I, II, or III Mediastinitis after an unsuccessful treatment attempt
Type IVB	Type I, II, or III Mediastinitis after multiple unsuccessful treatment attempts
Type V	Mediastinitis seen for the first time six weeks or more postoperatively

Table 2. The classification of sternal infections by anatomical region and recommended muscle flap

Wound type	Sternal wound site	Recommended muscle flap
Type A	Upper half of the sternum	Pectoralis major muscle
Type B	Lower half of the sternum	Pectoralis major muscle and rectus abdominis muscle
Type C	Entire sternum	Pectoralis major muscle and rectus abdominis muscle

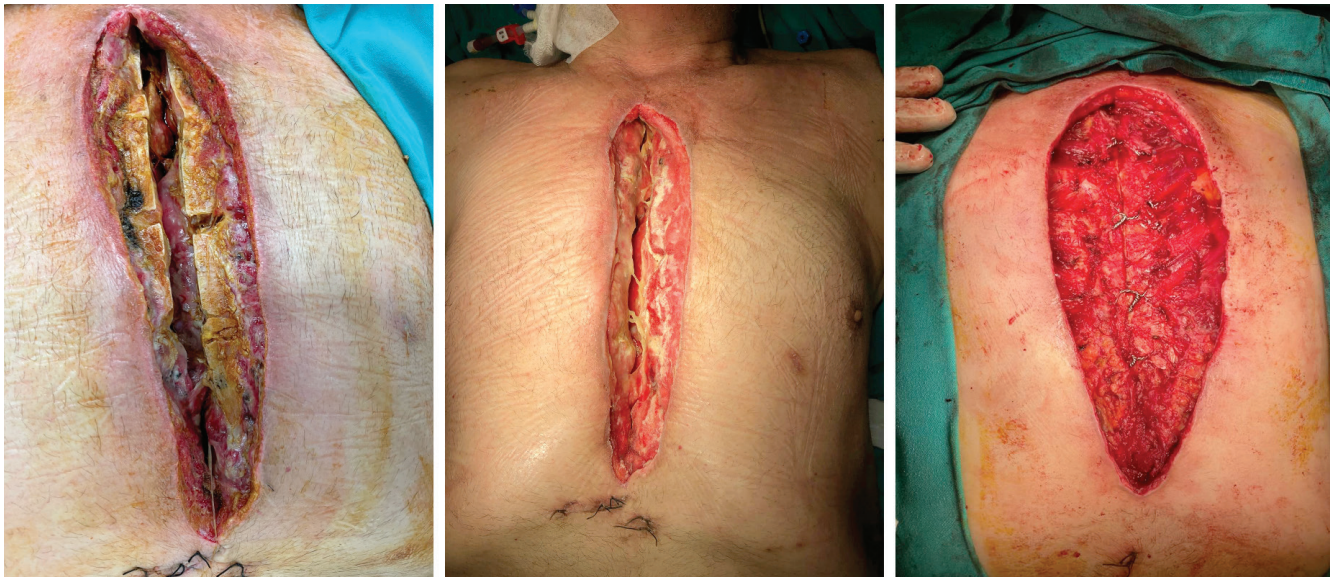

Figure 1. Preoperative photos of different patients with deep mediastinal infection before serial debridement.

subcutaneous tissues and sternum. Cultures were obtained from both the bone tissue and subcutaneous tissue during the initial debridement. Vacuum-assisted wound closure system was used in all patients after the debridement. Repeated debridements were performed at 48-72 hour intervals and vacuum-assisted wound closure systems were renewed. The application of a vacuum-assisted wound closure system was continued until a negative culture result was detected and granulation tissue developed in the wound in clinical terms. Among the patients who had negative blood cultures and developing granulation tissue, those with tissue losses that did not reach the sternum incision sites were evaluated in terms of flaps together with plastic and reconstructive surgery, and wound closure was performed with a pectoral muscle flap (Figure 2). The rectus abdominis muscle was also used as a flap in two patients. The pectoral muscle was separated from the area where it was attached to the sternum up to the level of the nipple during the preparation of the pectoral muscle flaps,

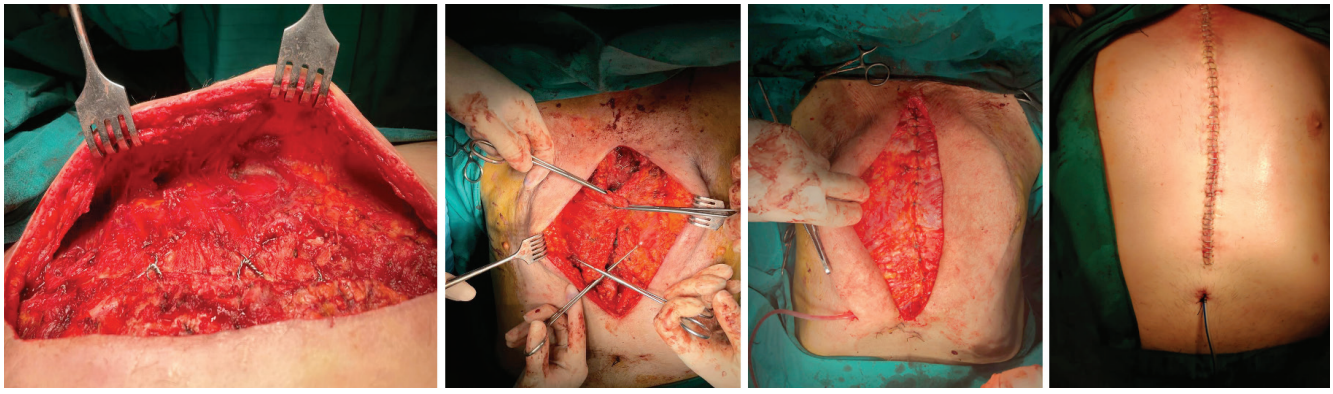

Figure 2. Treatment of pectoral muscle flap.

and the area of attachment to the humerus was preserved. The sternum incision was extended towards the umbilicus, the anterior rectus fascia was opened and the muscle was released during the preparation of the rectus muscle flap. In the right and left chest where the muscle flaps were taken, a hemovac drain was applied under the skin, and a perforated gauze cloth saturated with soft Paraffin with 5% Chlorhexidine acetate was applied on the incision site. The hemovac drains were removed in patients without drainage and dressings were continued every other day. All patients were followed for one year.

Statistics

Continuous variables were represented as mean ± standard deviation (SD) in the present study and the SPSS 18.0 (SPSS Inc., Chicago, Illinois) package software was used for descriptive statistics.

RESULTS

Among the patients, 14 (66.6%) were female and 7 (33.3%) were male, with a mean age of 62.7 ± 6.5 (range: 41-76 years). According to the Classification of Mediastinitis defined by El Oakley and Wright, three of the 21 patients included in the study had type I, two had type II, and 16 had type IIIA Mediastinitis. According to the anatomical region classification, eight patients had type A, nine had type B, and four had type C mediastinitis. A total of 14 had coronary artery bypass surgery, four had a mitral valve replacement, two had an aortic valve replacement, and one had mitral valve replacement surgery with aortic valve replacement. Seventeen patients (81%) were operated on under elective conditions, and four patients (19%) were operated on under emergency conditions. Sternal separation was detected in three patients. The mean time to the onset of the signs of infection in the patients was 9.2 days. The clinical and demographic characteristics of the patients are summarized in Table 3.

In all patients who were included in the study, acute phase reactants were found to be high in the examinations performed. Although there was discharge at the incision site in all patients, fever was detected high in 15 patients, and fever was not observed in six patients during their follow-ups. Parameters on the follow-up and treatment of these patients are summarized in Table 4.

Out of the patients, four (19%) experienced serous discharge at the sternum incision sites, while 17 patients (81%) exhibited purulent discharge. Among the patients, three (14.3%) had growth in the culture from the discharge, 16 patients (76.2%) had growth in the culture from the subcutaneous tissue, and two patients (9.5%) had growth in the culture from the bone tissue. When the isolated pathogenic microorganisms were examined, *Staphylococcus aureus* (*S. aureus*) was the most isolated microorganism with 11 patients (52.3%) and coagulase-negative *staphylococci* (three patients, 14.3%), *Escherichia coli* (two patients, 9.5%), *Acinetobacter* spp. (two patients, 9.5%), *Klebsiella pneumoniae* (one patient, 4.8%), *Streptococcus pneumoniae* (one patient, 4.8%), and *Pseudomonas aeruginosa* (one patient, 4.8%) were isolated. Upon examining the antibiogram sensitivity of one of the two patients with isolated *Acinetobacter* spp. and the patient with isolated *Klebsiella* pneumoniae, the treatment regimen was switched from Vancomycin + Meropenem to Tigecycline + Meropenem due to the observed resistance.

Pectoral muscles were used as flaps in the treatment of patients to fill the tissue spaces formed after serial debridements and vacuum-assisted wound closure system applications and to enable the sternum incision to approach each other. Partial sternum resection was performed in two patients with growth in cultures taken from sternal tissue. The sternum was fixed by rewire in one patient with sternal dehiscence and partial sternum resection was performed in the other two patients, and the remaining sternum was fixed using steel wire. Depending on the size and location of the tissue spaces, the right pectoralis major muscle was used in four patients (19%), the left pectoralis major muscle in four patients (19%), and the bilateral pectoralis major

Table 3. The clinical and demographic characteristics of the patients

Characteristics	Number of patients (n)	Percentage (%)
Age	62.7 ± 6.5	
Gender		
Male	7	33.3
Female	14	66.7
Mediastinitis Type		
Type I	3	14.3
Type II	2	9.5
Type IIIA	16	76.2
Anatomical Mediastinitis Class		
Type A	8	38.1
Type B	9	42.9
Type C	4	19
Patient with Sternal Separation	3	14.2
Additional Disease and Risk Factors		
Smoking	16	76.2
DM	12	57.1
HT	14	66.7
Obesity (BMI>30 kg/m^2)	9	42.9
COPD	7	33.3
CRI	2	9.5
Peripheral artery disease	3	14.2
Type of Surgery		
Urgent	4	19
Elective	17	81
Surgery		
Coronary artery by-pass graft	14	66.7
Mitral valve replacement	4	19
Aortic valve replacement	2	9.5
Aortic valve replacement + Mitral valve replacement	1	4.8

DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, CRI: Chronic renal insufficiency, BMI: Body mass index.

muscle in 13 patients (62%). The rectus abdominis muscle and pectoralis major muscle were used as flaps in two of four patients who were classified as type C Mediastinitis according to the anatomical classification. The use of the rectus abdominis muscle as a flap was not needed because the pectoralis major muscle flaps were sufficient to close the tissue space in type B Mediastinitis cases. Surgical flap closure was performed after an average of 16.7 days from the onset of the symptoms and emergency flap closure was not performed in any patient.

After the pectoral muscle flap surgery, the patients were followed up in the intensive care unit for one day, and during this period, one patient (4.8%) needed a repeat surgery because of bleeding in the area where the muscle flap was taken. No complications developed again after the bleeding control and no wound dehiscence/healing or re-infection were detected in any patient.

Table 4. The follow-up and treatment parameters of mediastinitis patients

Characteristics	Number of Patients (n)	Percentage (%)
Flow Type		
Serous	4	19
Purulent	17	81
Place of Sampling with Reproduction in Culture		
Flow	3	14.3
Subcutaneous tissue	16	76.2
Bone	2	9.5
Pathogen Microorganism		
Staphylococcus aureus	11	52.3
Coagulase-negative staphylococci	3	14.3
Escherichia coli	2	9.5
Acinetobacter spp.	2	9.5
Klebsiella pneumoniae	1	4.8
Streptococcus pneumoniae	1	4.8
Pseudomonas aeruginosa	1	4.8
Use of vacuum-assisted closing system	21	100
Flap Used		
Right pectoralis major	4	19
Left pectoralis major	4	19
Bilateral pectoralis major	13	62
Complication		
Bleeding	1	4.8
Wound separation/Non-healing	0	0
Re-infection	0	0
Treatment success	21	100
Mortality	0	0

Success was achieved in all 21 patients treated with pectoral muscle flap because of deep mediastinal infection and all patients were followed for one year. There was no need for re-intervention in the follow-up of the patients. No mortality was reported among the patients who received treatment, either due to infection, surgical muscle flap closure, or cardiac causes.

DISCUSSION

As a result of the development of advanced diagnosis and interventional examinations in patients with cardiac complaints, the number of patients undergoing cardiac surgery has also increased. The increased rate of cardiac surgery has naturally led to sternal wound infections becoming a more common condition in this patient population. These sternal infections may present with a serious manifestation such as mediastinitis, or they may be seen as superficial simple infections[15]. When the literature was reviewed, the incidence of deep sternal wound infections varies between 2% and 4%[16] and was found to be 3.6% in the present study.

The causative agent may be different pathogens in Mediastinitis cases. In a study on deep mediastinal infections by Sommerstein et al., *S. aureus*, coagulase-negative *staphylococci*, and gram-negative bacteria were the most common pathogens in etiology[16]. In a study that included 3896 patients who had undergone cardiac surgery, it was reported that the most frequently isolated microorganism in Mediastinitis cases was *S. aureus* with a rate of 32%, followed

by coagulase-negative *staphylococci* with a rate of 29.6%[17]. In another study that was conducted in our country, coagulase-negative *staphylococci* were in first place with 38.2% of microorganisms that were isolated from patients treated for mediastinitis, *Klebsiella* was in second place with 14.7%, and S. *aureus* was in the third place with 13.2%[18]. In the present study, similar to the literature, the most common pathogenic microorganisms were found to be *S. aureus* (52.3%) and coagulase-negative *staphylococci* (14.3%).

The treatment methods used in patients with Mediastinitis are debridement, open or closed drainage, antibiotherapy, partial sternal resection, vacuum-assisted wound closure system applications, and muscle flap closure applications[15]. The first step is the initiation of appropriate antibiotic therapy and removal of infected tissue from the area in treatment. In this way, the purpose is to protect heart tissue, vascular grafts, implanted valves, and used patches from infection. Although there are researchers who advocate early flap treatment in the treatment of deep mediastinal infections, there are also opinions advocating the use of vacuum-assisted therapies as bridging therapy before the flap treatment[19]. We used the vacuum-assisted wound closure system as a bridging treatment until the flap treatment by debridement in the early period. We believe that this bridging treatment is the reason for achieving a completely infection-free area and the absence of recurrent infections in all our patients.

In terms of mortality, in a study conducted in 2013, Aydın et al. applied negative vacuum therapy to 22 patients with deep mediastinal infection and closed mediastinal irrigation therapy was applied to 19 patients in addition to antibiotherapy. Although none of the patients who underwent vacuum-assisted therapy died, it was reported that three patients died[20]. It was reported in another study that three (16.6%) of 16 patients who underwent muscle flap treatment for Mediastinitis died[17]. In another study conducted with 7973 patients who underwent open heart surgery at Tampere University Hospital between 2006 and 2017, 129 (1.6%) of the patients had a deep mediastinal infection in the postoperative period, and 26 patients (20.2%) died in the one-year follow-up of these patients[21]. Kachel et al. reported that they used sternoplasty for the treatment of 68 mediastinitis patients and the mortality rate was 2.9%[22]. In the present study, all patients with deep mediastinal infection were debrided by starting antibiotherapy in the early period, and bridging treatment was applied to the patients with vacuum-assisted closure until negative wound culture and granulation tissue were detected. Then, closure was performed with a pectoral muscle flap. During the one-year follow-up period of our patients, no cases of re-infection, need for re-intervention due to wound deterioration, or mortality were observed among any of the patients. Effective antibiotherapy and debridement were started in the early period in patients with mediastinitis. We believe that the multidisciplinary approach involving infectious diseases, plastic, and reconstructive surgery has had a significant impact on the success of the treatment process. In the literature, studies report that closure with a pectoral muscle flap has unsuccessful results leading to re-separation in sternal wounds involving the lower 1/3 of the sternum[23]. Another study reported that the unilateral pectoralis major flaps have been a good option for the reconstruction of the sternal wound[24]. Elassal et al. reported that the pectoral flap is a less invasive method for most reconstructive procedures[25]. Although it is recommended for patients with type B mediastinitis, the researchers successfully performed the closure with the pectoralis major muscle without the need to use a rectus abdominis flap. Although the researchers were successful in this, the small number of patients and the fact that it was a single-centered study were the limitations of the study. We believe that conducting multicenter studies involving a larger number of patients can potentially yield more significant results in this regard.

In conclusion, although mediastinitis, in other words, deep sternal infections, is less common, it can cause high morbidity and mortality. Treatment and care of patients who develop Mediastinitis is a complex, long-term, and costly treatment requiring prolonged hospitalization, and may result in mortality. As a result, the primary objective should be to prevent the development of mediastinitis, and it is crucial to initiate prompt and effective treatment in patients who do develop mediastinitis. We believe that this process should be carried out through a multidisciplinary approach, involving collaboration between cardiovascular surgery, infectious diseases, and plastic and reconstructive surgery units.

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Non-invasive Clinical Research Ethics Committee (Decision no: 18, Date: 26.07.2022).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - All of authors; Analysis/Interpretation - CO, ASK; Data Collection - CO, ASK, AEK; Writing - All of authors; Critical Revision - All of authors; Final Approval - All of authors; Statistical Analysis -CO, ASK; Overall Responsibility - CO.

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

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Balloon Angioplasty to Great Saphenous Vein Graft Interposed in RUDI

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ABSTRACT

Vascular access-induced ischemia is an arteriovenous fistula (AVF) complication that can be treated surgically by interposing grafts to improve distal flow. However, over time, the interposed grafts may occasionally experience narrowing, which may require surgical or endovascular interventions for treatment. In this case report, we present a patient who underwent balloon angioplasty to address the narrowing observed in the great saphenous vein graft that had been interposed during a Revision Using Distal Inflow (RUDI) procedure.

Key Words: Arteriovenous fistula; balloon angioplasty; dialysis; ischemia

RUDI İşleminde İnterpoze Edilen Safen Ven Greftine Balon Anjiyoplasti

ÖZET

Damar erişim yolu nedenli iskemi, arteriyovenöz fistül (AVF) yapılan hastalarda görülebilecek bir komplikasyondur. Bu komplikasyon, distal akımı sağlayacak bir greft interpozisyonu ile cerrahi olarak tedavi edilebilir. Fakat interpoze edilen greftler de zamanla tıkanabilir, bu durumun da cerrahi veya girişimsel işlemlerle tedavi şansı vardır. Bu olgu sunumunda, distal girişi kullanılarak yapılan revizyon (*revision using distal inflow*-RUDI) işleminde interpoze edilmiş olan safen ven greftinde daralma sonrası gerçekleştirilen balon anjiyoplasti vakası sunulmaktadır.

Anahtar Kelimeler: Arteriyovenöz fistül; balon anjiyoplasti; diyaliz; iskemi

INTRODUCTION

Arteriovenous fistula (AVF) remains to be the recommended type of vascular access (VA). Still, it may cause significant complications which may be challenging to manage. VA-induced ischemia is an AVF complication with a reported incidence of up to 30%, describing distal hypoperfusion resulting in ischemia that can be limb- and life-threatening[1]. Revision using distal inflow (RUDI) is one of the relatively novel techniques performed to treat VA-induced ischemia surgically[2]. Still, complications may be observed occasionally regarding the interposed graft, which can be addressed via endovascular interventions. In this case report, we present a patient who had undergone balloon angioplasty due to the narrowing in the great saphenous vein graft which had been interposed in a RUDI procedure.

CASE REPORT

A 65-year-old man with end-stage renal disease (ESRD) had undergone a left brachiocephalic AVF (BCAVF) operation in an external medical center in September 2021. After one month, the patient was admitted to our clinic with a two-week history of ulceration on the fingertips. His hand was cold, and he had resting pain in his hand. Radial and ulnar pulses were diminished. The duplex ultrasound examination revealed a flow rate of nearly 1050 mL/min in the AVF. The arterial vasculature was normal in radial and ulnar arteries and no significant stenosis was observed. Manual compression of the AVF resulted in a temporary improvement in capillary refill time, warming of the hand, and pain relief. He was diagnosed with VA-induced ischemia, and a RUDI procedure was planned. Preoperative mapping of upper and lower limb vasculature was performed with duplex ultrasound by the operating surgeon. A 4-5 cm autogenous graft with a diameter of 5 mm was

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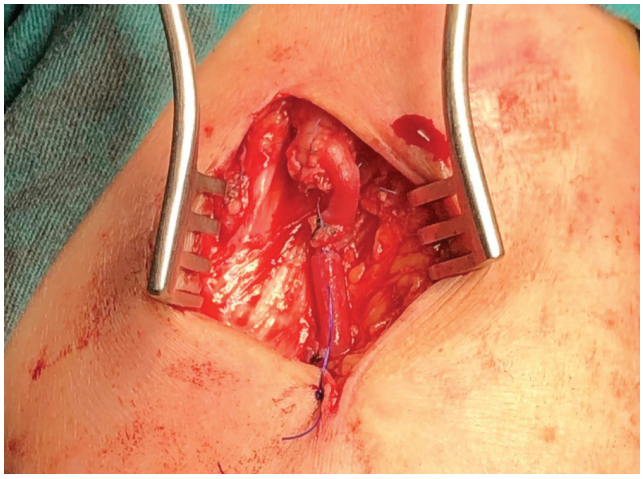

Figure 1. The harvested great saphenous vein graft was interposed between the proximal radial artery and cephalic vein.

excised from the left great saphenous vein, which had been partially harvested during a previous coronary artery bypass graft surgery. The current BCAVF was closed surgically and the harvested saphenous vein graft was interposed between the proximal radial artery and cephalic vein (Figure 1), both anastomoses were done in an end-to-side fashion. Postoperatively, the hand regained warmth and the ischemic symptoms showed regression. The patient was admitted to our clinic due to an inadequate flow rate, which hindered efficient hemodialysis, after two months of successful hemodialysis sessions. A duplex ultrasound examination revealed a narrowing in the saphenous vein graft, and a percutaneous transluminal angioplasty (PTA) was planned. The angiography confirmed the narrowing (Figure 2-a). Pre-dilatation was performed using a regular 5 mm PTA balloon catheter (Admiral Extreme; Invatec/Medtronic, Frauenfeld, Switzerland) for a duration of three minutes. Subsequently, a 6 mm paclitaxel-coated balloon catheter (IN.PACT Admiral, Medtronic, Santa Rosa, California) was inflated for five minutes. The narrowing was dilated successfully (Figure 2-b). The flow rate in the saphenous vein graft was 200 mL/min and 500 mL/min before and after the PTA, respectively. The patient remained symptom-free at the end of his three-month clinical follow-up period, and the ulcerations regressed (Figure 3). Furthermore, the patient has been successfully undergoing hemodialysis sessions since the endovascular intervention. It is important to note that informed consent has been obtained from the patient for the publication of the case report and the accompanying images.

DISCUSSION

VA-induced ischemia is a limb-threatening complication of AVF that requires prompt management to prevent further ischemia[3]. Treatment options for VA-induced ischemia have expanded over time with the introduction of new surgical approaches. Surgical modalities that can be employed to address VA-induced ischemia include AVF ligation, banding, distal revascularization with interval ligation (DRIL), proximalization of the arterial inflow (PAI), and revision using distal inflow (RUDI)[4,5]. Ligation is one of the oldest techniques suggested

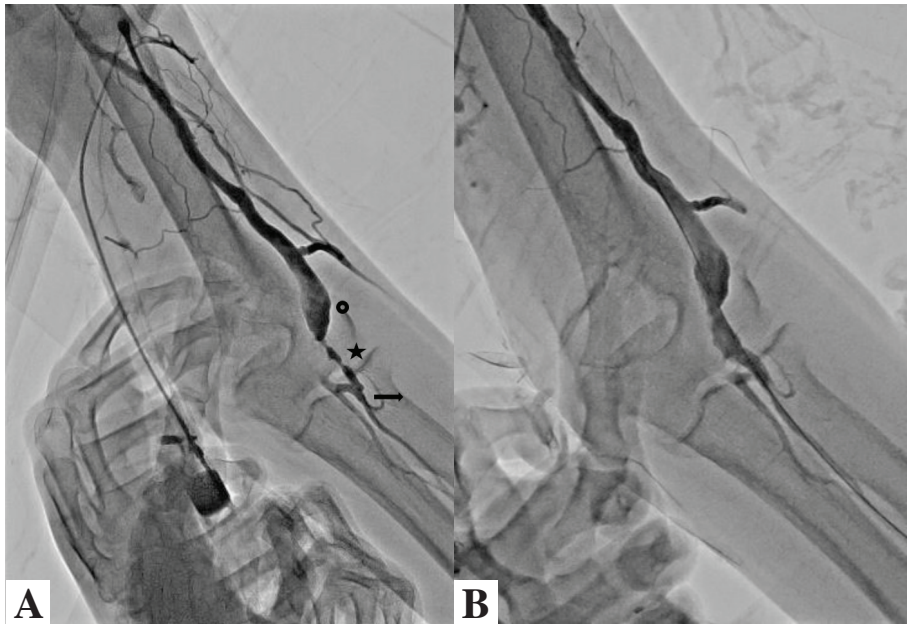

Figure 2. Narrowing in the great saphenous vein graft **(A)** before and **(B)** after balloon dilatation. Circle: Cephalic vein, star: Saphenous vein graft, arrow: radial artery. Since the image reflects reflux angiography, the brachial artery and the cephalic vein were compressed with the hand. This is the reason why the operator's hand can be seen in the X-ray beam.

Figure 3. The ischemic symptoms regressed after balloon angioplasty.

to treat VA-induced ischemia, which offers satisfactory rates of symptom improvement, but leaving the patient with no access is a major disadvantage[4].

DRIL is the ligation of the artery below the AVF anastomosis and forming a bypass conduit from a more proximal arterial source[5]. It is one of the most commonly preferred modalities that preserve access, which offers long-term secondary patency rates up to 80%[1]. Still, the complex nature of the DRIL procedure requires general anesthesia and a relatively long operative time, and thus the general condition of the patient should be evaluated cautiously, and the patient selection should be made accordingly[4]. Moreover, the native arterial vasculature is altered via the DRIL procedure and the perfusion of the hand, which is already suffering from ischemia, being dependent on a bypass graft remains a concern[1].

Whereas, RUDI is a relatively novel method, which includes ligation of the AVF at its origin and recreation of the fistula via interposing bypass graft between more distal arterial source and vein[2]. The procedure is applied to BCAVFs mostly and the most commonly used distal artery in RUDI operations is the proximal radial artery[3], as done in our case. Angiography may be performed prior to surgery in selected cases. However, we did not prefer an angiography in this case because we did not doubt significant stenosis with the Duplex ultrasound examination. Prosthetic material such as polytetrafluoroethylene (PTFE) or autogenous grafts harvested from the great saphenous vein, cephalic vein, or basilic vein can be utilized as conduit materials. Autogenous grafts are more commonly preferred due to better long-term patency, easier cannulation, lower infection rates, and superior cost-effectiveness[3]. RUDI operations may present higher postoperative bleeding risk[4] and lower postoperative AVF flow rate compared to DRIL[1]. Still, RUDI presents similar rates of patency, symptom relief, and survival with DRIL, and it is favorable, especially in higher flow fistulas[1].

A recent review revealed that VA-induced ischemia was resolved in 82% of the patients who were treated with RUDI and that the primary AVF was protected over a median of 1 year[3]. However, some complications such as thrombosis in AVF, digit-amputation, or permanent ischemic neuropathy can be seen[3]. Patients may present with stenosis in arteries or veins, which can be treated via endovascular interventions or surgery. A single-center study demonstrated that most of the cases requiring angioplasty were perianastomotic or outflow vein stenosis, similar to the observations in our case, which were seen in both RUDI and DRIL at comparable rates[1].

CONCLUSION

RUDI is a safe and reasonable surgical method for treating VA-induced ischemia with similar rates of patency and symptom relief compared to other treatment modalities. Interposed graft problems may emerge after RUDI operations, which can be fixed successfully via angioplasty techniques.

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