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Effects of calcific and inflammatory mechanisms on different aortic cusps in etiopathogenesis of degenerative aortic stenosis

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ABSTRACT

Objectives: This study aimed to evaluate pathological differences in aortic valve cusps from patients undergoing aortic valve replacement due to aortic stenosis.

Patients and methods: In this single-blind observational study, aortic valves from 20 patients (10 males, 10 females; mean age: 69±6.36 years; range, 62-84 years) were divided into left coronary, right coronary, and noncoronary cusps between January 2013 and December 2014. The cusps were stabilized in 10% formalin and sent to the pathology lab in a blinded manner. Sections 5 µm in thickness were prepared, stained with hematoxylin-eosin and Van Gieson, and analyzed for inflammation, fibrosis, and calcification using light microscopy. Comparisons were made between right, left, and noncoronary cusps.

Results: Inflammation comparisons between right, left, and noncoronary cusps showed no statistically significant differences ($p=0.199$, $p=0.789$, and $p=0.379$, respectively). For fibrosis, left and right coronary cusps and right and noncoronary cusps were not significantly different ($p=0.079$ and $p=0.880$); however, the comparison between left coronary and noncoronary cusps was significant ($p=0.046$). Regarding calcification, left and right coronary cusps and right coronary and noncoronary cusps showed no significant difference ($p=0.285$ and $p=0.180$), while the comparison between left coronary and noncoronary cusps was statistically significant ($p=0.011$).

Conclusion: While pathological differences between aortic valve cusps are rarely emphasized in the literature, this study identified significant fibrosis and calcification differences in left coronary and noncoronary cusps. These findings could contribute to a better understanding of calcific aortic stenosis and potentially guide new treatments.

Keywords: Aortic stenosis, calcification, fibrosis, inflammation.

Aortic stenosis is a major indication for valve replacement surgeries in Türkiye, with degenerative calcific aortic stenosis more common in older patients.^[1] While acute rheumatic fever remains the primary cause of aortic stenosis in younger populations, degenerative aortic stenosis in older adults results from idiopathic calcification and atherosclerosis, often affecting individual valve cusps without fusion.^[2,3] This form of the disease is now recognized as part of a systemic atherosclerotic process, with lipid deposits, inflammation, and calcification as primary pathological features.^[4-7] Calcification, a hallmark of degenerative aortic stenosis, is typically localized to the aortic side of the valve cusps and plays a central role in disease progression.^[5,8]

The progression of aortic stenosis shares similarities with atherosclerosis, with endothelial damage due to mechanical stress playing a key role. The distribution

of lesions on the valve is influenced by factors such as tangential tension, which varies across the cusps, and mechanical stress at attachment sites on the aortic root.^[9] This damage triggers localized inflammation and calcification, processes regulated by inflammatory cytokines, oxidative stress, and lipoprotein metabolism.^[4-6]

Advanced imaging techniques, such as computed tomography (CT), are critical for quantifying

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calcification and evaluating the severity of aortic stenosis.^[8,10] These techniques have been shown to correlate with disease progression, particularly in patients with elevated lipoprotein (a) levels.^[6,11-13]

Despite advances in imaging and understanding of disease mechanisms, the precise pathophysiology remains unclear, and medical therapies to slow progression are still unavailable.^[5,6] Therefore, identifying reliable indicators of disease progression and the need for surgical intervention is crucial. This study aimed to evaluate the pathological effects of degenerative aortic stenosis on different valve cusps using samples from aortic valve replacement surgeries performed in our clinic.

PATIENTS AND METHODS

The single-blind observational study was conducted with 20 patients (10 males, 10 females; mean age: 69±6.36; range, 62-84 years) who underwent aortic valve replacement due to degenerative calcific aortic stenosis at the Cardiovascular Surgery Clinic of the Celal Bayar University between January 2013 and December 2014. Patients with the history of rheumatic fever, congenital aortic stenosis, and bicuspid valves were excluded. Written informed consent was obtained from all patients. The study protocol was approved by the Celal Bayar University Faculty of Medicine Ethics Committee (date: 10.12.2012, no: 20,478,486,246). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Aortic valve surgery was performed in standard fashion with single stage cannulation following median sternotomy. The removed valve was divided into left coronary, right coronary, and noncoronary cusps. It was then fixed in 10% buffered formalin solution. When the total number of valves reached 20 and the number of cusps reached 60, the cusps were numbered from 1 to 60 in a mixed manner and sent to the pathology laboratory. While the surgical clinic knew the number that identified each cusp, the pathology clinic remained blinded. The cusps that were observed to be excessively calcified in manual examination of the valves were kept in decalcification solution for 12 h and remaining for 1 h and were subjected to routine tissue follow-up in a fully automatic tissue tracking device without any further action. At the end of this process, the valves were placed on one surface and embedded in paraffin

in a way to provide the widest possible examination through the embedding device. Sections of 5 µm in thickness were taken from the tissue blocks obtained in this way by means of a standard rotary microtome, and these sections were stained with hematoxylin-eosin and Van Gieson after deparaffinization and rehydration.

Sections stained with hematoxylin-eosin were examined under a standard light microscope by a blinded, expert pathologist and evaluated for calcification, fibrosis, and inflammatory infiltration. A score of 1 was assigned if areas of calcification and fibrosis were less than 25% of the cusp surface, 2 if between 25% and 50%, and 3 if more than 50%.^[1] Sections stained with Van Gieson were also used to determine the fibrosis score, and cell-free type 1 collagen areas stained with bright red were considered fibrosis areas (Figure 1).

In order to determine the level of inflammatory infiltration, absence of inflammatory cells (lymphocytes or plasma cells) was considered Grade 0, presence of rare inflammatory cells scattered on the section surface or a single group of no more than 20 inflammatory cells was identified as Grade 1, the presence of more than one group of more than 20 inflammatory cells on the surface was classified as Grade 2, and the presence of more than 20 groups or a group of more than 100 cells was considered Grade 3 (Figure 2).

In addition, CD3 (clone SP7, 1/150 dilution, incubation time 30 min; Thermo Fisher Scientific, Waltham, MA, USA), CD20 (clone L26, 1/200 dilution, incubation time 30 min; BioCare, Concord, CA, USA), CD4 (clone 4B12, prediluted, incubation time 60 min; DAKO, Denmark ApS, Glostrup, Denmark), CD8 (clone SP16, 1/100 dilution, incubation time 60 min; Thermo Fisher Scientific, Waltham, MA, USA), and CD138 (clone MI15, prediluted, incubation time 40 min; Thermo Fisher Scientific, Waltham, MA, USA) were added for six cusps with Grade II and III inflammation. All immunohistochemical studies were performed with the Ventana fully automatic immunostaining device (Roche Diagnostics, Rotkreuz, Switzerland) and standard kits for this machine.

Statistical analysis

Data were analyzed using IBM SPSS version 19 software (IBM Corp., Armonk, NY, USA).

Table 1
Cross-tables of calcification degrees, fibrosis grades, and inflammation degrees by cusp types

	Calcification degree			Fibrosis grades			Inflammation degree			
	1	2	3	1	2	3	0	1	2	3
Right-coronary cusp										
Frequency	6	2	12	2	8	10	5	13	2	0
%	30.0	10.0	60.0	10.0	40.0	50.0	25.0	65.0	10.0	0.0
Left-coronary cusp										
Frequency	8	4	8	5	10	5	1	17	2	0
%	40.0	20.0	40.0	25.0	50.0	25.0	5.0	85.0	10.0	0.0
Non-coronary cusp										
Frequency	1	4	15	1	9	10	5	12	2	1
%	5.0	20.0	75.0	5.0	45.0	50.0	25.0	60.0	10.0	5.0
Total										
Frequency	15	10	35	8	27	25	11	42	6	1
%	25.0	16.7	58.3	13.3	45.0	41.7	18.3	70.0	10.0	1.7

Student's t-test was used to determine mean values and standard deviations, and the Mann-Whitney test was used for nonparametric tests. The distribution of the data according to the cusp type was analyzed through cross tables. A p-value <0.05 was considered statistically significant.

RESULTS

Right coronary and left coronary cusps were compared based on calcification, fibrosis and inflammation. The results are given in Table 1. The z-value for the degree of calcification was -1.069 ($p=0.285$), the z-value for the degree of fibrosis was -1.759 ($p=0.079$), and the z-value for the degree of inflammation was -1.285 ($p=0.199$). There was no difference between the two valve types in terms of these features.

Right coronary and noncoronary cups were also compared (Table 2). While the z-value for the degree of calcification was 1.341 ($p=0.180$), the z-value for the fibrosis degree was -0.151 ($p=0.880$), and the z-value for the degree of inflammation was -0.267 ($p=0.789$). It was determined that there was no difference between the two valve types in terms of these features.

Finally, left coronary and noncoronary cusps were compared (Table 2). The z-value for the degree of calcification was -2.555 ($p=0.011$), the z-value for the degree of fibrosis was -1.995 ($p=0.046$), and

the z-value for the degree of inflammation was -0.880 ($p=0.379$). The degree of calcification and fibrosis yielded statistically significant results for the comparison of left coronary and noncoronary cusps.

DISCUSSION

Calcific aortic stenosis constitutes the leading class of valve diseases in the Western world. In the past 10 years, the number of aortic valve replacement surgeries performed in some countries has doubled according to the literature. Considering the increasing elderly population, it is predicted that cases of aortic stenosis will double again in the next 20 years.^[14]

Although surgical aortic valve replacement is common, transcatheter aortic valve implantation is an alternative treatment method in patients with severe aortic stenosis, particularly those at high risk for surgical aortic valve replacement.^[15] As the number of transcatheter aortic valve implantation procedures increases, understanding the pathology of aortic disease becomes more important. Calcification degrees should be assessed before procedures, and specific measures should be taken.^[16-18]

This progressive disease is characterized by inflammation, fibrosis, and calcification, with the latter often serving as a primary marker of disease severity.^[5,8] Advanced imaging modalities such as CT allow for accurate assessment of calcification, which is

Table 2
Comparison of right coronary, left coronary, and noncoronary cusps

	Right-coronary/left-coronary valves			Right-coronary/non-coronary cusps			Left-coronary and non-coronary cusps		
	Calcification degree	Fibrosis degree	Inflammation degree	Calcification degree	Fibrosis degree	Inflammation degree	Calcification degree	Fibrosis degree	Inflammation degree
Mann-Whitney U test	164	140	164	159	195	191.5	116	132.5	174.5
According to Wilcoxon test									
W	374	350	374	369	405	401.5	326	342.5	384.5
Z	-1.069	-1.759	-1.285	-1.341	-0.151	-0.267	-2.555	-1.995	-0.88
Asymp. sig. (2-tailed)	0.285	0.079	0.199	0.18	0.88	0.789	0.011	0.046	0.379
Exact sig. [2*(1-tailed Sig.)]	0.341	0.108	0.341	0.277	0.904	0.820	0.023	0.068	0.495

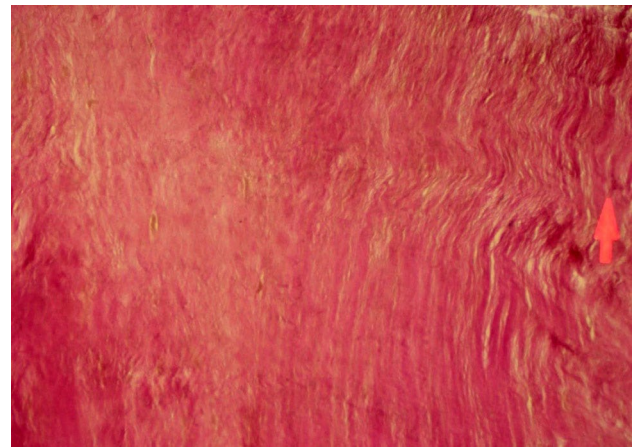


Figure 1. Van Gieson-stained sections were used to determine the fibrosis score, and cell-free type 1 collagen areas stained with bright red were considered as fibrosis areas (Van Gieson ×200).

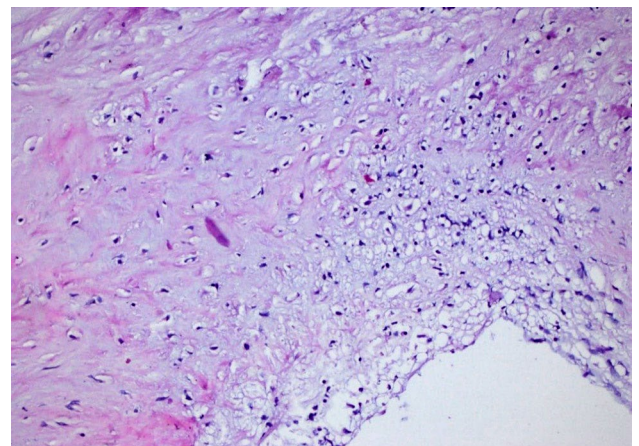


Figure 2. Grade 3 inflammation (H&E, ×200).

crucial for evaluating disease severity and prognosis.^[8,10] The role of lipoprotein (a) is particularly noteworthy, as elevated levels have been shown to correlate with faster calcification progression and worse outcomes.^[6] Recent evidence suggests that lipoprotein (a) mediates calcification via oxidative stress and inflammatory pathways, underscoring its importance as a therapeutic target.^[6] Furthermore, inflammatory regulation of extracellular matrix remodeling and immune cell infiltration have also been implicated in disease progression.^[2,5]

Left ventricular afterload increases due to the progressive narrowing of the aortic valve. In the face of the increasing pressure load, myocytes initiate a

hypertrophic process. While this process initially reduces the stress on the wall, it is later insufficient. In patients with aortic stenosis, the emergence of symptoms related to the progression of the disease, the observance of adverse effects, and the need for surgery depend on the narrowing of the valve and the resulting left ventricular hypertrophy.^[19,20]

In calcific aortic stenosis, the valves become progressively thickened, fibrotic, and calcified. As a result, valve stiffness, decreased movement, and narrowing of the valve opening are observed in contrast to the fusion that develops in rheumatic valve diseases. Historically, calcific aortic stenosis was thought to be caused by wear and age-related degeneration after prolonged use. However, recent evidence shows that aortic stenosis occurs as a result of active inflammation involving biochemical, humoral, and genetic factors.

Although the differences were not statistically significant in our study, we believe that it is mainly due to the limited number of patients. Radiological examinations are effective in determining the calcification levels of the aortic cusps; however, there is still no definite answer about the underlying process. As we expand our knowledge on the etiopathogenesis of the disease, the management of treatment will also advance. Although pathological differences between aortic cusps rarely take part in current literature, we believe that it will shed light on new developments in medical and surgical treatment of calcific aortic stenosis.

This study was limited by its small sample size. Larger studies incorporating advanced imaging and molecular biomarkers, as recommended in recent literature, are needed to validate these findings and inform clinical practice.^[8,10]

In conclusion, these findings emphasize the role of lipoprotein metabolism, advanced imaging techniques, and inflammation in disease progression. Understanding these mechanisms could guide new medical and surgical therapies aimed at improving patient outcomes.

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Fibrosis-4 index is related to left atrial volume index in patients with acute coronary syndrome

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ABSTRACT

Objectives: This study aims to evaluate the predictive value of fibrosis-4 (FIB-4) index and left atrial (LA) indices in patients with acute coronary syndrome (ACS).

Patients and methods: Between September 2023 and March 2024, a total of 300 consecutive patients with ACS (244 males, 56 females; mean age: 62.7±11.7 years; range, 49 to 78 years) were included in the study. The study group was divided into two groups according to the LA volume index (LAVI) measurements as those with <34 mL/m² (Group 1, n=226) and those with ≥34 mL/m² (Group 2, n=74). Demographic, clinical and laboratory data of the patients were recorded.

Results: Among a total of 300 patients, 25.6% (n=77) were diagnosed with ST-elevation myocardial infarction (STEMI), 54% (n=162) with non-STEMI (NSTEMI), and 20.3% (n=61) with unstable angina pectoris (USAP). The FIB-4 index was positively associated with the LAVI (odds ratio [OR]=6.419; 95% confidence interval [CI]: 1.505-27.38; p=0.012). In addition, elevated FIB-4 index could predict a LAVI of ≥34 mL/m² (area under the curve [AUC]: 0.705, p<0.001).

Conclusion: An elevated FIB-4 index is correlated with increased LAVI scores, which may serve as a well-established indicator of adverse outcomes and a reliable measure of cardiovascular risk in patients with ACS.

Keywords: Acute coronary syndrome, fibrosis-4 index, left atrial volume index.

Acute coronary syndrome (ACS) significantly contributes to cardiovascular disease (CVD)-related mortality. It encompasses a spectrum of disorders, including acute myocardial infarction (MI) and unstable angina pectoris (USAP) and all of them are marked by significant myocardial damage.^[1]

The atrial, particularly the left atrium (LA), size and function have a robust role in the clinical assessment of various cardiac conditions.^[2] In daily practice, LA size is typically assessed by measuring the diameter obtained anteroposterior image.^[3] Owing to the asymmetrical nature of the LA, volumetric measurements offer a more precise indication of its size compared to evaluations based solely on diameter or area. To evaluate the size of the LA, the preferred method involves calculating the LA volume and normalizing it to the body surface area.^[4] Research has shown that, among the various parameters for evaluating cardiac organ damage, the LA volume index (LAVI) stands out for most discriminating measure.^[5]

Moreover, LAVI has emerged as a robust predictor of increased mortality risk, exhibiting independent significance from left ventricular (LV) geometry in a population with preserved systolic function.^[6] Left ventricular diastolic dysfunction, induced by ventricular hypertrophy, arterial hypertension, and other cardiovascular (CV) conditions, results in elevated filling pressures and structural alterations in the atria owing to sustained pressure overload.^[7] Researchers have suggested that the LAVI can be used to assess the intensity and longevity of diastolic dysfunction. Additionally, LAVI was identified to be potential

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indicator of adverse clinical outcomes including embolic stroke, atrial fibrillation (AF) development, and heart failure.^[8] Various previous trials have shown that LAVI can predict major unfavorable cardiac events during hospitalization and beyond.^[9,10]

The increasing prevalence of non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome has led to their recognition as common liver disorders on a global scale. The former affects various organs outside the liver, including the CV system.^[11] Clinical studies have demonstrated that NAFLD plays a contributory role for accelerating the atherogenic process and the association between CVD and NAFLD is causative or both diseases result from a common pathogenic origin.^[12] Notably, NAFLD patients with an increased risk of progressive fibrosis are particularly at a higher risk for CVD, which significantly contributes to adverse event rates in this group of patients. Fibrosis in the liver not only affects the liver, but also initiates an inflammatory process throughout the body.^[13] Additionally, studies indicate that as fibrosis progresses in the liver, there is an increase in the fibrotic process in the heart.^[14] Current guidelines strongly advise the utilization of non-invasive markers and scoring systems to determine the prognostic risk associated with liver-related conditions.^[15] The diagnostic protocol should incorporate a basic assessment, through the Fibrosis-4 (FIB-4) or NAFLD score, for better predicting of possible advanced fibrosis, as recommended by established guidelines.^[16] Aspartate transaminase, alanine transaminase, and platelet levels and patient age are used to calculate the FIB-4 index which is straightforward, non-invasive, and valuable instrument for estimating fibrosis.

Previous research has shown a convincing association between FIB-4 index and atherosclerotic process, besides AF and CV events.^[17] However, its relationship with LAVI, particularly, has not been elucidated yet. In the present study, we hypothesized that the FIB-4 index, a score associated with cardiac preload, could also correlate with the LAVI, a parameter influenced by this preload. We, therefore, aimed to evaluate the predictive value of FIB-4 index and LA indices in ACS patients.

PATIENTS AND METHODS

This single-center, cross-sectional, observational cohort study was conducted at Recep Tayyip Erdoğan

University Faculty of Medicine, Department of Cardiology between September 2023 and March 2024. A total of 300 consecutive patients with ACS (244 males, 56 females; mean age: 62.7±11.7 years; range, 49 to 78 years) were included in the study. In accordance with the current guidelines,^[18] multiple factors, such as 12-lead electrocardiogram (ECG) results, cardiac-related symptoms, and increased levels of blood markers indicating myocardial necrosis, were used to diagnose ACS. For patients experiencing typical chest discomfort and suspected of having ACS, the diagnosis of ST-elevation MI (STEMI) was established when the ECG revealed ST-segment elevation in two adjacent leads. Non-ST elevation MI (NSTEMI) was identified in cases where the ECG lacked ST elevation, but troponin levels exceeded the 99th percentile. Unstable angina pectoris was characterized by myocardial ischemia occurring during rest or minimal physical activity without evidence of acute cardiomyocyte damage or death. Exclusion criteria were as follows: a substantial decline in renal function (estimated glomerular filtration rate [eGFR] below 30 mL/min/1.73 m²), moderate-to-severe heart valve disease, chronic alcohol consumption, severe hematological disorders, active inflammatory diseases, malignancy, having a diagnosis or previous history of bile duct obstruction, liver transplantation, acute or chronic viral hepatitis, taking any medication that may affect aspartate transaminase, alanine transaminase and platelet count, and extremely frail elderly patients. A written informed consent was obtained from each patient. The study protocol was approved by the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee (date: 12.09.2023, no: 2023/203). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic and laboratory data

Lipid panel assessments were derived from blood samples acquired after a 12-h fasting period, whereas other laboratory analyses were performed using venous blood samples acquired upon admission to the emergency department. Diabetes mellitus and hypertension were defined according to current guidelines.^[19,20] Hyperlipidemia was defined as either a prior diagnosis of hypercholesterolemia or the use of previous or current cholesterol-lowering therapies. Demographic and clinical data, including age, sex, and medication use, was documented. The definition of smoking included individuals who consumed at least one cigarette daily. The FIB-4 index

was calculated using a formula that incorporates commonly measured laboratory values: FIB-4 index: (age [years] × aspartate transaminase [U/L]) / (platelet count [$\times 10^9/L$] × square root of alanine transaminase [U/L]).^[21]

Echocardiographic evaluation

All participants undertook through two-dimensional transthoracic echocardiography conducted with a Philips EPIQ 7 device (Philips Medical Systems, Andover, MA, USA) utilizing an X5-1 transducer operating at a frequency range of 1 to 5 MHz. In accordance with the established guidelines, late diastolic peak flow velocity (A) and

early diastolic peak flow velocity (E) were measured at the tips of the mitral leaflets using pulse-wave Doppler echocardiography. Two-dimensional M-mode echocardiographic images were gained to measure the LA and LV diameters. The LV ejection fraction (LVEF) was calculated using the modified Simpson's method.^[22] Early (Em) and late (Am) diastolic velocities of the mitral annulus were obtained by tissue Doppler echocardiography. During end-diastole at parasternal long-axis view, the thickness of both the LV posterior wall and the interventricular septum (IVS) was measured.

The area-length method was utilized to measure LA volume using the apical two- and four-

Table 1
Baseline demographic and clinical data of patients

Variables	LAVI <34 mL/m ² (n=226)					LAVI ≥34 mL/m ² (n=74)					p
	n	%	Mean±SD	Median	25 th -75 th percentiles	n	%	Mean±SD	Median	25 th -75 th percentiles	
Demographic data											
Sex											
Male	196	86.7				48	64.9				<0.001
Age (year)			60.8±10.9					68.6±11.6			<0.001
BMI (kg/m ²)			29.1±4.7					29.6±4.9			0.356
SBP (mmHg)			131.9±22.4					134.6±22.3			0.379
DBP (mmHg)			77.6±13.2					76.7±14.5			0.645
HT	122	54				57	77				<0.001
DM	83	36.7				35	47.3				0.030
HPL	96	42.5				26	35.1				0.059
Current smoking	109	48.2				17	23.0				<0.001
PAD	9	4.0				5	6.8				0.144
CVA	10	4.4				6	8.1				0.106
STEMI	95	42.0				31	41.9				0.108
Previous CABG	9	4.0				10	13.5				0.005
Previous PCI	43	19.0				14	18.9				0.135
Killip class >I	8	3.6				7	9.5				0.035
FIB-4 index				1.6	1.16-2.40				2.2	1.5-3.3	<0.001
Medication usage data (prehospital)											
ASA	52	23.6				17	23.0				0.073
Beta blocker	41	18.1				9	12.2				0.154
ACE-i	28	12.4				13	17.6				0.175
ARB	30	13.3				10	13.5				0.958
P2Y12 inhibitor	10	4.4				3	4.1				0.258

LAVI: Left atrium volume index; SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HT: Hypertension; DM: Diabetes mellitus; HPL: Hyperlipidemia; PAD: Peripheral arterial disease; CVA: Cerebrovascular accident; STEMI: ST-elevation myocardial infarction; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention; FIB-4: Fibrosis-4; ASA: Aspirin salicylic acid; ACE-i: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

chamber views with dismissing of LA appendage and pulmonary veins from the measurements. To obtain the LAVI in mL/m², the LA volume was divided by the body surface area. Body mass index was calculated by dividing weight in kg by the square of height in cm. A LAVI above 34 mL/m² was considered to indicate an abnormally enlarged LAVI.^[4] The study group was divided into two groups according to the LAVI measurements as those with <34 mL/m² (Group 1, n=226) and those with ≥34 mL/m² (Group 2, n=74).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD) or median (25th-75th percentiles), while categorical variables were expressed in number and frequency. Normality of distribution of the variables was checked using the Shapiro-Wilk or Kolmogorov-Smirnov test. A univariate logistic regression analysis was used to identify

Table 2
Comparison of echocardiographic, angiographic, and laboratory data

Variable	LAVI <34 mL/m ² (n=226)			LAVI ≥34 mL/m ² (n=74)			p
	Mean±SD	Median	25 th -75 th percentiles	Mean±SD	Median	25 th -75 th percentiles	
Echocardiographic data							
LVEF (%)	53.6±9.7			49.2±12.5			0.002
IVS (mm)	11.6±1.6			12.5±1.9			0.001
PW (mm)	10.8±1.5			11.6±1.5			<0.001
E (cm/s)	67.5±17.2			85.4±27.2			<0.001
A (cm/s)	85.1±20.6			74.7±44.1			<0.001
Em (cm/s)	6.4±2.1			6.7±2.1			0.497
Am (cm/s)	8.8±2.2			6.4±3.6			<0.001
E/Em ratio	11.1±3.6			13.6±5.1			<0.001
E/A ratio	0.80±0.30			0.96±0.46			0.005
Angiographic data							
Stent count (n)	1.2±0.5			1.3±0.7			0.136
Stent length (n)	25.7±11.3			27.8±13.7			0.178
Lesion count (n)	1.2±0.5			1.2±0.6			0.710
Prevalence of CAD (n)	1.3±0.6			1.6±0.8			0.004
Laboratory data							
Glucose (mg/dL)	148.3±72.9			166.1±83.9			0.081
Serum creatinine (mg/dL)	0.90±0.29			1.03±0.36			0.180
Total cholesterol (mg/dL)	157.7±11.4			192.8±41.5			0.444
HbA1c (%)	6.5±1.5			6.9±1.8			0.153
Peak troponin (Ng/dL)	23.1±21.1			25.5±20.7			0.456
e-GFR (mL/min/1.73 m ²)	80.9±20.1			70.9±23.1			<0.001
WBC (10 ³ /μL)	10.1±3.3			10.1±3.4			0.969
Hemoglobin (gr/L)	14.5±1.7			13.1±2.1			<0.001
CRP (mg/dL)		0.63	0.35-1.30		0.99	0.52-2.20	<0.001

LAVI: Left atrium volume index; SD: Standard deviation; LVEF: Left ventricular ejection fraction; IVS: Interventricular septum wall thickness; PW: Posterior wall thickness; E: Early diastolic peak flow velocity; A: Late diastolic peak flow velocity; Em: Early mitral annular diastolic velocity; Am: Late mitral annular diastolic velocity; CAD: Coronary artery disease; HbA1c: Hemoglobin A1c; eGFR: Estimated glomerular filtration rate; WBC: White blood count; CRP: C-reactive protein.

parameters which significantly differed. A multivariate logistic regression analysis incorporating statistically significant *p* values into the model was conducted. Receiver operating characteristic (ROC) analysis was carried out to calculate the sensitivity and specificity of the FIB-4 index in predicting high LAVI patients. The Spearman or Pearson correlation tests were also employed to evaluate the association of the FIB-4 index and LAVI. A *p* value of <0.05 was considered statistically significant.

RESULTS

Among a total of 300 patients, 25.6% (n=77) were diagnosed with STEMI, 54% (n=162) with NSTEMI, and 20.3% (n=61) with USAP. Group 1

had a LAVI of <34 mL/m² and Group 2 had a LAVI of ≥34 mL/m². Baseline demographic and clinical data of the patients are summarized in Table 1. The mean prevalence of coronary artery disease (CAD) was significantly higher in Group 2 (p=0.004) (Table 2). Paradoxically, individuals with normal LAVI measurements were found to have a higher incidence of smoking (p<0.001). The median FIB-4 index levels were higher in Group 2 (2.2 [1.5-3.3] vs. 1.6 [1.16-2.40], p<0.001). Figure 1 demonstrates the strong relationship between the FIB-4-index and LAVI (p<0.001). Correlation analysis revealed a significant positive correlation between the FIB-4 index and LAVI (r=0.238, p<0.001), indicating that elevated FIB-4 index score was associated with enlarged LAVI (Figure 2).

Table 3
Univariate and multivariate logistic regression analysis results

Variables	Univariate			Multivariate		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Age	1.063	1.037-1.090	<0.001			
Sex						
Male	0.283	0.153-0.521	<0.001			
Hypertension	2.858	1.566-5.216	<0.001			
Diabetes mellitus	1.546	0.910-2.682	0.107			
Current smoking	0.320	0.175-0.584	<0.001	0.292	0.117-0.732	0.009
Previous CABG	3.767	1.468-9.671	0.006			
Killip class >I	2.834	0.991-8.104	0.052			
Prevalence of CAD	1.668	1.172-2.432	0.005	1.819	1.112-2.975	0.002
FIB-4 index (log)	4.552	1.81-11.5	0.001	6.419	1.505-27.38	0.012
LVEF	0.966	0.943-0.989	0.003	0.956	0.927-0.987	0.005
IVS	1.339	1.150-1.558	<0.001	1.549	1.255-1.913	<0.001
PW	1.457	1.211-1.753	<0.001			
E	1.040	1.025-1.055	<0.001			
A	0.998	0.979-1.007	0.009			
Am	0.742	0.668-0.825	<0.001			
E/Em	1.142	1.072-1.216	<0.001			
E/A	2.809	1.318-5.984	0.004	4.283	1.691-10.849	0.002
GFR	0.979	0.967-0.991	<0.001			
Hemoglobin	0.686	0.591-0.797	<0.001	0.689	0.559-0.834	<0.001
CRP	2.313	1.287-4.157	0.005			

OR: Odds ratio; CI: Confidence interval; CABG: Coronary artery bypass graft; CAD: Coronary artery disease; FIB-4: Fibrosis-4; LVEF: Left ventricular rejection fraction; IVS: Interventricular septum wall thickness; PW: Posterior wall thickness; E: Early diastolic peak flow velocity; A: Late diastolic peak flow velocity; Am: Late mitral annular diastolic velocity; Em: Early mitral annular diastolic velocity; eGFR: Estimated glomerular filtration rate; CRP: C-reactive protein.

Predictor	OR	95% CI	p
Smoking	0.292	0.117-0.732	0.009
Prevalence of CAD	1.819	1.112-2.975	0.002
FIB-4 index (log)	6.419	1.505-27.38	0.012
LVEF	0.956	0.927-0.987	0.005
IVS	1.549	1.255-1.913	<0.001
E/A ratio	4.283	1.691-10.849	0.002
Hemoglobin	0.689	0.559-0.834	<0.001

OR: Odds ratio; CI: Confidence interval; CAD: Coronary artery disease; FIB-4: Fibrosis-4; LVEF: Left ventricular ejection fraction; IVS: Interventricular septum wall thickness; E: Early diastolic peak flow velocity; A: Late diastolic peak flow velocity.

Comparing echocardiographic data between the groups, significant differences were observed in terms of LV wall thicknesses (Table 2). Comparing laboratory values, the mean eGFR and hemoglobin levels were lower in Group 2 ($p < 0.001$ for both). However, there was an elevation in C-reactive protein (CRP) levels in Group 2, indicating a statistically significant difference ($p < 0.001$). On the other hand, the mean peak troponin levels were comparable between the groups ($p = 0.437$).

The univariate analysis was carried out to identify parameters which significantly differed between the groups (Table 3). In the multivariate analysis, smoking status (odds ratio [OR]=0.292, 95% confidence interval [CI]: 0.117-0.732; $p = 0.009$), CAD history (OR=1.819, 95% CI: 1.112-2.975; $p = 0.002$), FIB-4

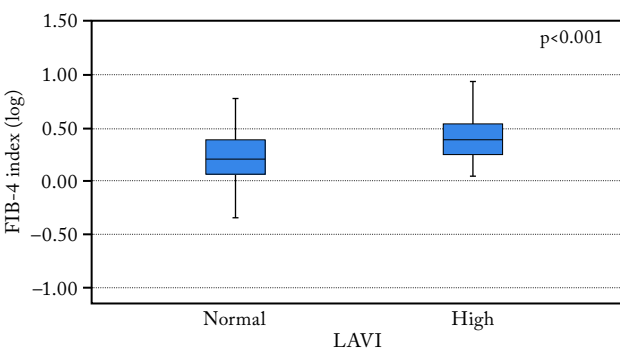


Figure 1. Graph showing the strong relationship between LAVI and FIB-4-index.
LAVI: Left atrium volume index; FIB-4: Fibrosis-4.

index (OR=6.419, 95% CI: 1.505-27.38; $p = 0.012$), LVEF (OR=0.956, 95% CI: 0.927-0.987; $p = 0.005$), IVS thickness (OR=1.549, 95% CI: 1.255-1.913; $p < 0.001$), E/A ratio (OR=4.283, 95% CI: 1.691-10.849; $p = 0.002$), and hemoglobin levels (OR=0.689, 95% CI: 0.559-0.834; $p < 0.001$) were independent predictors of increased LAVI (Table 4). The ROC analysis showed that the area under the curve (AUC) for the FIB-4 index was 0.705 ($p < 0.001$) (Figure 3).

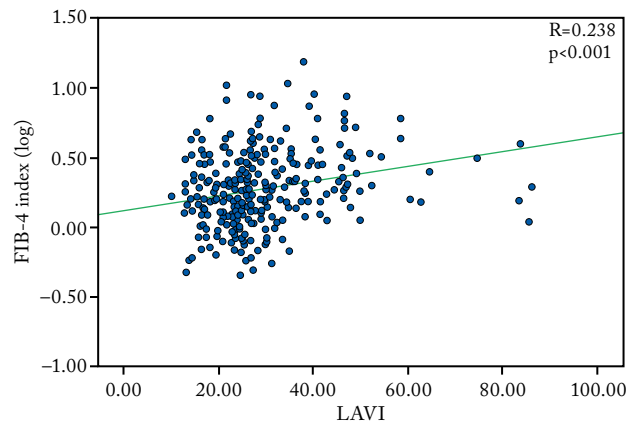


Figure 2. Correlation analysis of LAVI and FIB-4-index.
LAVI: Left atrium volume index; FIB-4: Fibrosis-4.

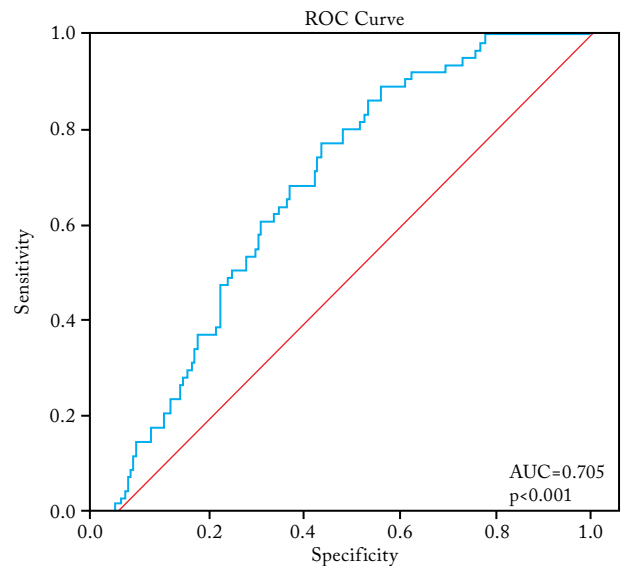


Figure 3. ROC analysis showing that a higher FIB-4 index could predict LAVI ≥ 34 mL/m², with an AUC of 0.705 ($p < 0.001$).
ROC: Receiver operating characteristic; FIB-4: Fibrosis-4; LAVI: Left atrium volume index.

DISCUSSION

In the present study, we investigated the relationship concerning FIB-4 index and LAVI in ACS patient cohort. Our study results showed that the FIB-4 index was independently correlated with the increased LAVI. This novel relationship indicates that the FIB-4 index may function as a precious instrument in evaluating the risk and predicting outcomes in ACS. Although a considerable improvement has been made in ACS diagnosis and treatment in recent years, the incidence of major adverse cardiac events continues to be substantial.^[23] The prognosis varies largely based on the extent of LV damage. Therefore, timely risk evaluation of these patients is essential. Moreover, in our study, prevalence of CAD, lower LVEF, IVS thickness, E/A ratio, and lower hemoglobin levels were significant predictors of high LAVI. More intriguingly, there was a significantly higher smoking rate in the low LAVI group.

As the configuration, utility, and function of the LA deteriorate, the LA pressure increases, which is reflected in the pulmonary capillaries, and the impact of the LA to the LV reduces.^[24] Therefore, LAVI is of utmost importance for the early recognition of impaired LA function. In our study, LAVI, which indicates an increase in LA pressure, and the FIB-4 index, which is indirectly related to this condition, were positively correlated.

It has been demonstrated that NAFLD is not only a hepatic disorder, but also a systemic disease and is considered a significant risk factor for diabetes mellitus, metabolic syndrome, and CVD.^[11] A study showed significant alterations in the LV function and structure due to NAFLD, despite the lack of overt CVD.^[25] In addition, multiple studies and meta-analyses have consistently revealed a link between NAFLD and various CV issues such as increased carotid intima-media thickness, cardiomyopathy, diminished endothelial function, arrhythmias, and heightened arterial stiffness.^[26] These results emphasize the significance of recognizing and addressing CV consequences of NAFLD to enhance patient management and outcomes. This can be attributed to various processes such as chronic mild inflammation, oxidative damage, inflammatory proteins, and reduced insulin sensitivity, all of which promote atherosclerosis.^[14,27] Moreover, patients with NAFLD have a likelihood of CV complications, including heart failure and acute MI, as evaluated using the FIB-4

index.^[28] The presence of proven non-invasive markers makes quick diagnosis more practicable and, if they provide additional predictive value, can also aid in the prevention of CVD. The FIB-4 index is useful in the CV area for predicting unfavorable outcomes, such as readmission to the hospital and death from all causes among heart failure patients.^[29] Moreover, an elevated FIB-4 index has been associated with an increased incidence of all-cause mortality in patients with acute MI.^[30] Additionally, a recent study demonstrated a substantial correlation between the FIB-4 index and LAVI, LV diastolic and end-systolic diameters, E/Em ratio, deceleration time, and maximal inferior vena cava diameter in patients with significant tricuspid regurgitation without other valve involvement.^[31]

Distortion of the cardiac fiber structure across each stratum indicates enhanced myocardial stress under the conditions of hyperdynamic circulation attributed to splenic arterial vasodilatation and a decrease in systemic vascular resistance in patients with cirrhosis.^[32] Diastolic dysfunction has been identified as a prompt marker of cirrhotic cardiomyopathy and may be characterized by four variables: E/Em ratio, mitral annular velocities, tricuspid regurgitation velocity, and LAVI.^[33]

The high LAVI group in our study exhibited impacts on both the LV systolic and diastolic parameters. Strong predictors of high LAVI included a reduction in LVEF and an elevation in the E/A ratio. Also, LA enlargement determined by echocardiography may be regarded as a reliable prognosticator of LV systolic and diastolic dysfunction, as LA represents the filling pressure of LV. Similarly, an increase in LA size compared to controls has been previously demonstrated in patients with NAFLD, suggesting a relationship with the disease severity of the disease.^[34] It has been also proposed that LA remodeling serves as a proxy for diastolic load and a predictor of CV events, such as heart failure, new-onset AF, or CV death.^[35] The possible mechanisms include an elevated inflammatory burden and a proatherogenic environment. Furthermore, a connection between NAFLD and LV diastolic dysfunction has been proposed, potentially leading to LA enlargement through diverse pathways.^[36]

In the current study, smokers had a significantly lower LAVI compared to non-smokers. This paradoxical finding can be explained by several mechanisms.

Chronic sympathetic activation due to smoking can induce atrial fibrosis, reduce atrial compliance, and limit the volume expansion. Additionally, smoking-related endothelial dysfunction and reduced nitric oxide bioavailability may contribute to increased atrial stiffness. Furthermore, elevated pulmonary vascular resistance and altered LV filling dynamics can impair the LA preload, leading to a lower LAVI.^[37] These findings suggest that smoking may influence atrial remodeling through mechanisms distinct from conventional risk factors which warrants further investigation.

In previous studies, LAVI has been established as a prognostic indicator of ACS. It redirects the cumulative overload of high filling pressures over time and, therefore, does not necessarily reflect sudden drops in cardiac function.^[38] Since LAVI reflects subacute or chronic alterations in diastolic function, it is less responsive to abrupt fluctuations.^[39] Our study results suggest that a high FIB-4 index is associated with an elevated LAVI in patients with ACS. Additionally, the relationship between the FIB-4 index and AF has been demonstrated in different studies.^[40] This may be due to the onset and progression of the fibrotic process in the LA along with the progression of the fibrotic process in the liver and the simultaneous progression of LA pressure in a chronic process.

Nonetheless, this study has several limitations. First, this study was conducted at a single center, and the sample size was relatively small. Further multi-center, large-scale studies are needed to confirm these findings. Second, we did not use any imaging or biopsy procedures to confirm the presence of NAFLD. Further studies utilizing imaging techniques may yield additional outcomes on this subject. Third, echocardiography was the sole method used for cardiac imaging in this study. Future research may involve various imaging techniques such as computed tomography or cardiac magnetic resonance imaging. Furthermore, it would be reasonable to conduct a non-invasive risk estimation study on ACS patients with a larger sample size. Another important limitation is the lack of data on the relationship between the FIB-4 index and clinical outcomes. Finally, since our study is a cross-sectional study, we were unable to follow the patients in the long term. Collecting data by following these patients in the long term may reveal different data regarding the relationship between the FIB-4 index and LAVI.

In conclusion, FIB-4 index has emerged as a basic and non-invasive scoring tool capable of predicting elevated LAVI, a well-established indicator of adverse outcomes and risk quantification, in patients with ACS. However, further well-designed studies are warranted to draw more reliable conclusions on this subject.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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The effect of Killip class on the development of anxiety in intensive care unit patients with acute myocardial infarction

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ABSTRACT

Objectives: This study aims to investigate the effect of Killip class on the development of anxiety and depression in patients admitted to intensive care unit (ICU) with acute myocardial infarction (AMI) and to identify risk groups in terms of anxiety and depression.

Patients and methods: Between May 2024 and October 2024, a total of 200 patients (140 males, 60 females; mean age: 61.4±12.1 years; range, 31 to 89 years) with acute ST elevation MI (STEMI) and non-ST elevation MI (NSTEMI) were included. The Hospital Anxiety and Depression Scale (HADS) was administered within the first 24 h after the patients' treatment in the ICU was completed and the patients were transferred to ward.

Results: Anxiety was observed in 60 (30%) of the patients, while depression was observed in 93 (46.5%) of the patients. A total of 148 (74%) of the patients were Killip in Class I, while the others had a class other than Killip I. Having a class other than Killip I and prolonged ICU stay significantly increased the anxiety scores ($p=0.003$ and $p=0.016$). In the univariate and multivariate regression analysis, having a classification other than Killip I was found to be an independent predictor of ICU anxiety (odds ratio [OR]=0.456; 95% confidence interval [CI]: 0.210-0.993; $p=0.048$).

Conclusion: Killip classification is an independent predictor of anxiety in AMI patients. Since patients with AMI, particularly those who are in Killip Class II-IV, are in the risk group for anxiety, it is of utmost importance to evaluate the anxiety status of these patients as soon as possible and to reduce the affecting factors by identifying them.

Keywords: Acute myocardial infarction, anxiety, depression, intensive care unit.

Cardiovascular diseases are one of the major causes of morbidity and mortality in Türkiye and in the world.^[1] According to the World Health Organization (WHO) and Turkish Statistical Institute (TurkStat) data, ischemic heart disease is the leading cause of death, which reveals the importance of investigating this disease in every aspect.^[1,2]

Acute myocardial infarction (AMI) not only affects the quality of life of patients, but also causes psychological problems. Anxiety is common in patients with AMI during the acute phase. One of the main causes of anxiety is the fear of death. In addition, severe angina and other symptoms experienced by patients, hospitalization and related stressors can also cause anxiety, as patients feel that their health and life goals are threatened. While anxiety is at the forefront in patients in the first days, depression is more common in the following days. Post-AMI depression

may be associated with the uncertainty experienced by individuals, physical limitations, anxiety about loss of function, anxiety about not being able to continue social life, and feelings of guilt about their past life.^[3-5]

While AMI can cause psychological problems, psychological comorbidities which occur in patients can adversely affect the treatment process. Intense anxiety triggers activation of the sympathetic nervous system and increases the release of hormones such as adrenaline and cortisol, causing an increase in heart

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rate and blood pressure and increasing the workload of the heart, which can cause a more severe course of physical disease. Additionally, anxiety and depression may cause problems in adaptation to the primary disease. Due to these effects, providing psychological support to patients with high levels of anxiety and depression may improve the prognosis and reduce the rate of rehospitalization. In addition to the physical recovery process in these patients, their psychological states should also be carefully monitored.^[3,6]

Killip classification is a classification system used to clinically evaluate the hemodynamic status of patients with AMI and to identify the risk of mortality.^[7] It consists of four classes. Killip Class I is the lowest class with mortality risk (6%) without signs of heart failure. In Killip Class II, ventricular gallop rhythm (S3) and wet crackles can be seen in the lung bases, while in Killip Class III, there is acute pulmonary edema and the risk of mortality is around 38% and in Killip Class IV, the mortality risk (80%) is the highest class in which cardiogenic shock is seen.^[7] Considering that the level of anxiety experienced by patients will differ depending on the severity of the disease and the nature of the symptoms, it is thought that the levels of anxiety and depression experienced by patients in different classes of AMI according to the Killip classification would vary.^[8]

In the present study, we aimed to investigate the effect of Killip class on the development of anxiety and depression in patients admitted to intensive care unit (ICU) with AMI and to identify risk groups in terms of anxiety and depression.

PATIENTS AND METHODS

This single-center, descriptive, cross-sectional study was conducted at Bakırçay University, Faculty of Medicine, Department of Cardiology between May 2024 and October 2024. Patients with acute ST elevation MI (STEMI) and non-ST elevation MI (NSTEMI) who met the universal definition of AMI were included. Inclusion criteria were as follows: being over 18 years of age, having been hospitalized in ICU for at least 24 h, and not having a diagnosis of depression or anxiety. Patients diagnosed with any psychiatric disease, those with limited cooperation, and those who developed impaired consciousness after AMI were excluded from the study. Finally, a total of 200 patients (140 males, 60 females; mean age: 61.4±12.1 years; range, 31 to 89 years) who

were hospitalized in the ICU with the diagnosis of AMI were recruited. A written informed consent was obtained from each patient. The study protocol was approved by the Bakırçay University, Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (date: 21.05.2024, no: 2024-1618). The study was conducted in accordance with the principles of the Declaration of Helsinki.

A data collection form including demographic and clinical characteristic data and laboratory results of the patients and the Hospital Anxiety and Depression Scale (HADS) were used. The data collection form contains a total of 27 questions and there are two sections in the form. The first section includes questions regarding sociodemographic characteristics such as age, sex, presence of hypertension, diabetes mellitus, hyperlipidemia, marital status, education, occupation, while the second section includes questions about descriptive characteristics specific to the patient's health status and ICU, such as type of admission to ICU, Killip class during admission, duration of angiography, duration of stay in ICU, status of mechanical ventilation, duration and method of mechanical ventilation, and previous stay in ICU.

The HADS scale contains 14 questions and the questions are scored on a four-point Likert scale. It has two subscales: HAD anxiety subscale (HAD-A) and HAD depression subscale (HAD-D). The HAD-A section assesses anxiety with seven questions and HAD-D section assesses depression with seven questions. Items 1, 3, 5, 6, 8, 10, 11 and 13 of the scale are for anxiety, and they gradually decrease and are scored as 3, 2, 1, 0. The other items 2, 4, 7, 9, 12 and 14 of the scale are for depression and are scored as 0, 1, 2, 3. When the scores of items 1, 3, 5, 7, 9, 11 and 13 for the Anxiety Subscale are added. For the Depression Subscale, the scores of items 2, 4, 6, 8, 10, 12 and 14 are added. The minimum score that patients can get from both subscales is 0, and the maximum score is 21. The cut-off points for the Turkish form of HADS were determined as 10 for the Anxiety Subscale (HAD-A) and 7 for the Depression Subscale.^[9]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. The suitability of numerical variables

for normal distribution was examined using the Kolmogorov-Smirnov test. The independent samples t-test was used to make comparisons between two groups of continuous variables. The relationship between categorical variables was examined using the Pearson chi-square or Fisher exact test. To identify

independent risk factors on the development of anxiety, parameters with a *p* value of <0.1 were evaluated in the univariate regression analysis. Those with a *p* value of <0.05 were included in the multivariate regression analysis. A *p* value of <0.05 was considered statistically significant.

Table 1
Demographic and clinical characteristics of patients

Variables	Anxiety score (n=140)						<i>p</i>	Depression score (n=107)						<i>p</i>
	Score ≤10			10< score <21				Score ≤7			7< score <21			
	n	%	Mean±SD	n	%	Mean±SD		n	%	Mean±SD	n	%	Mean±SD	
Age (year)			62.2±11.7			59.8±12.6	0.199			59.9±11			63.3±12.7	0.043
Sex														
Male	102	72.8		38	63.3		0.154	78	72.9		62	66.7		0.286
Hypertension	82	58.6		33	55		0.640	60	56.1		55	59.1		0.662
Diabetes mellitus	59	42.1		26	43.3		0.876	41	38.3		44	47.3		0.199
Hyperlipidemia	61	43.6		26	43.3		0.975	46	43		41	44.1		0.876
CKD	6	4.3		5	8.3		0.250	4	3.7		7	7.5		0.241
CVD	2	1.4		0	0		1	0	0		2	2.2		0.215
COPD	13	9.3		6	10		0.875	8	7.5		11	11.8		0.295
Smoking	73	52.1		38	63.3		0.144	60	56.1		51	54.8		0.861
Alcohol	28	20		13	21.7		0.789	25	23.4		16	17.2		0.282
Marital status-married	100	71.4		40	66.7		0.501	80	74.8		60	64.5		0.115
Educational background														
0	8	5.7		7	11.7			6	5.6		9	9.7		
1	86	61.4		35	58.3			59	55.1		62	66.7		
2	26	18.6		12	20		0.442	23	21.5		15	16.1		0.073
3	20	14.3		6	10			19	17.8		7	7.5		
CAG history	56	40		23	38.3		0.825	42	39.3		37	39.8		0.939
Previous hospitalization	106	75.7		46	76.7		0.885	84	78.5		68	73.1		0.374
Previous intensive care unit history	49	35		23	38.3		0.653	39	36.4		33	35.5		0.887
NIV	3	2.1		4	6.7		0.201	2	1.9		5	5.4		0.254
Mechanical ventilator	3	2.1		4	6.7		0.201	4	3.7		3	3.2		1
CPR	3	2.1		3	5		0.367	4	3.7		2	2.2		0.687
Use of inotropic agents	2	1.4		4	6.7		0.067	1	0.9		5	5.4		0.099
Intensive care period			1.95±1.3			2.58±2.4	0.016			1.8±0.9			2.52±2.2	0.003
Type of MI														
NONSTEMI	82	58.6		35	58.3			64	59.8		53	57		
Inferior	35	25		11	18.3			24	22.4		22	23.7		
Anterior	21	15		12	20		0.530	17	15.9		16	17.2		0.982
Others	2	1.4		2	3.3			2	1.9		2	2.2		
Type of treatment														
Medical	19	13.6		6	10.2			16	15		9	9.8		
PCI	111	79.3		47	79.7		0.652	84	78.5		74	80.4		0.423
Surgery	10	7.1		6	10.2			7	6.5		9	9.8		
Type of access														
Radial	52	37.1		18	30.5			38	35.5		32	34.8		
Femoral	88	62.9		41	69.5		0.371	69	64.5		60	65.2		0.914
Killip classification														
I	112	80		36	60		0.003	85	79.4		63	67.7		0.06
II, III, IV	28	20		24	40			22	20.6		30	32.3		

SD: Standard deviation; CKD: Chronic kidney disease; CVD: Cerebrovascular disease; COPD: Chronic obstructive pulmonary disease; CAG: Coronary angiography; NIV: Non-invasive mechanical ventilator; CPR: Cardiopulmonary resuscitation; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; Educational background: 0: Illiterate; 1: Primary education; 2: High school; 3: University.

RESULTS

Demographic and clinical characteristics of patients are summarized in Table 1. The mean anxiety score was 7.84 ± 4.9 and the mean depression score was 7.36 ± 4.8 . Anxiety was observed in 60 (30%) of the patients, and depression was observed in 93 (46.5%).

While 148 (74%) of the patients were in Killip Class I, the others had a class other than Killip I. Of the patients other than Killip I, 37 (71%) were in Killip II, 10 (19%) were in Killip III, and five (10%) were in Killip IV. A total of 115 (57.5%) of the patients had hypertension, 85 (42.5%) had diabetes mellitus, and 87 (43.5%) had hyperlipidemia. Of the patients, 117 (58.5%) had non-STEMI, 46 (23%) had inferior

MI, 33 (16.5%) had anterior MI, and four (2%) had other MI (Table 1).

Coronary angiography was performed via radial access in 70 (35%) patients and via femoral access in 130 (65%) patients. Seventy-two (36%) patients had previous ICU hospitalization experience. The mean ICU hospitalization time was 2.1 ± 1.7 (range, 1 to 12) days (Table 1).

Considering the factors affecting ICU anxiety, having a class other than Killip I and prolonged ICU stay significantly increased the anxiety score ($p=0.003$ and $p=0.016$, respectively). The factors which significantly increased the ICU depression score were determined as advanced age and prolonged

Table 2
Laboratory data of patients

Variables	Anxiety score (n=140)			Depression score (n=107)		
	Score ≤ 10	10 < score < 21	<i>p</i>	Score ≤ 7	7 < score < 21	<i>p</i>
	Mean \pm SD	Mean \pm SD		Mean \pm SD	Mean \pm SD	
FBG (mg/dL)	156.8 \pm 75.9	143.3 \pm 55.1	0.216	155.5 \pm 79.5	149.5 \pm 58.6	0.548
Urea (mg/dL)	37.9 \pm 16.4	50.6 \pm 47.6	0.816	35.6 \pm 13.6	48.6 \pm 40.4	0.052
Creatinine (mg/dL)	1.01 \pm 0.7	1.35 \pm 1.5	0.186	1.01 \pm 0.7	1.23 \pm 1.25	0.083
Sodium (mEq/L)	139.6 \pm 3.6	139.4 \pm 3.2	0.749	139.3 \pm 3.2	139.8 \pm 3.7	0.276
Potassium (mg/dL)	4.36 \pm 0.6	4.35 \pm 0.7	0.900	4.32 \pm 0.6	4.4 \pm 0.7	0.427
Calcium (mg/dL)	9.1 \pm 0.6	8.98 \pm 0.5	0.241	9.13 \pm 0.6	8.96 \pm 0.5	0.044
AST (IU/L)	47.4 \pm 60.3	65.6 \pm 96.7	0.107	49.5 \pm 61.1	56.7 \pm 85.5	0.491
ALT (IU/L)	26.1 \pm 21.6	31.8 \pm 25.5	0.100	27.7 \pm 24.4	27.9 \pm 21.3	0.948
Total cholesterol (mg/dL)	192.9 \pm 49.3	189.1 \pm 53.2	0.635	200.4 \pm 51.7	181.7 \pm 47.2	0.009
HDL-cholesterol (mg/dL)	38.5 \pm 10.1	38.6 \pm 13.1	0.993	38.6 \pm 9.9	38.5 \pm 12.3	0.917
LDL-cholesterol (mg/dL)	115.9 \pm 37.4	116.3 \pm 39.2	0.951	120.1 \pm 37.6	111.4 \pm 37.8	0.118
Triglycerides (mg/dL)	202.1 \pm 181.8	155.1 \pm 88.6	0.062	208.7 \pm 173.4	164.1 \pm 142.6	0.054
WBC ($\times 10^9/L$)	10.6 \pm 3.3	11.2 \pm 3.8	0.337	10.4 \pm 2.9	11.3 \pm 4.1	0.069
Hemoglobin (g/dL)	13.8 \pm 2.2	13.1 \pm 2.4	0.057	14.1 \pm 2.1	13.1 \pm 2.4	0.004
Hematocrit (%)	43.6 \pm 5.9	41.7 \pm 7.2	0.052	44.3 \pm 5.4	41.6 \pm 7.1	0.003
Platelet count ($\times 10^9/L$)	248.6 \pm 72.9	265.2 \pm 99.1	0.189	250.8 \pm 68.2	256.9 \pm 95.2	0.604
Hs-cTnT	637.1 \pm 1309	1224 \pm 2304	0.061	538.8 \pm 1251	1128 \pm 2039	0.010
HbA1c (%)	7.03 \pm 2.1	6.52 \pm 1.4	0.102	7 \pm 2.1	6.7 \pm 1.7	0.350
TSH (mU/L)	1.94 \pm 2.4	2.02 \pm 3.6	0.860	2.2 \pm 2.7	1.7 \pm 2.9	0.266
T4 (mU/L)	1.24 \pm 0.4	1.24 \pm 0.4	0.981	1.2 \pm 0.5	1.2 \pm 0.4	0.917
LVEF (%)	52.9 \pm 8.6	51.1 \pm 10.8	0.223	52.5 \pm 9.3	52.3 \pm 9.5	0.864

SD: Standard deviation; FBG: Fasting blood glucose; AST: Aspartate transaminase; ALT: Alanine aminotransferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; WBC: White blood cell; Hs-cTnT: High-sensitive cardiac troponin T; HbA1c: Hemoglobin A1c; TSH: Thyroid-stimulating hormone; LVEF: Left ventricular ejection fraction.

Table 3
Univariate and multivariate logistic regression analysis results

Variables	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Killip classification (II, III, IV)	0.375	0.193-0.727	0.004	0.456	0.210-0.993	0.048
Intensive care period	1.225	1.028-1.460	0.024	1.101	0.901-1.346	0.347
Use of inotropic agents	0.203	0.036-1.139	0.07			

OR: Odds ratio; CI: Confidence interval.

ICU stay ($p=0.043$ and $p=0.003$, respectively). While no significant parameter affecting the anxiety score was found among the laboratory data of the patients, depression score was significantly increased by low calcium, total cholesterol, hemoglobin and hematocrit and high troponin ($p=0.044$, $p=0.009$, $p=0.004$, $p=0.003$ and $p=0.01$, respectively) (Table 2).

In the univariate and multivariate regression analysis performed to identify the independent predictors of ICU anxiety, having a classification other than Killip I was found to be an independent predictor (odds ratio [OR]=0.456; 95% confidence interval [CI]: 0.210-0.993; $p=0.048$) (Table 3).

DISCUSSION

In the present study, we investigated the effect of Killip class on the development of anxiety and depression in patients admitted to ICU with AMI and identified risk groups in terms of anxiety and depression. Our study results showed that having a class other than Killip I was an independent risk factor for the development of ICU anxiety in patients with AMI.

To prevent ischemic heart diseases, which are the leading causes of death worldwide, all risk factors in the individual must be evaluated together. Previous studies have shown that the main independent risk factors for coronary artery disease (CAD) are being ≥ 45 years of age for men, being ≥ 55 years of age for women, being a smoker and having a chronic disease such as diabetes, hypertension and hypercholesterolemia.^[10] In our study, the presence of these risk factors was observed in the majority of patients. The mean age of the patients was 61.4 ± 12.1 years, 57.5% had hypertension, 42.5% had diabetes, 43.5% had hyperlipidemia and 55.5% were smokers, consistent with the literature.^[10]

In the current study, 70% ($n=140$) of the patients were male patients. Similar to our study, in the studies conducted by Özer et al.^[11] and Demirbaş and Kaya^[3] examining anxiety and depression in patients diagnosed with MI, most of the participants were male. According to the Cardiovascular Risk Factors in Turkish Adults (TEKHARF) study, coronary heart disease was more common in men and the incidence of coronary-related mortality was 5.7 per thousand in men and 3.6 per thousand in women.^[12]

Anxiety and depression are the most common psychological problems in patients with MI. In our study, according to the HADS questionnaire, the mean anxiety score of the patients was 7.84 ± 4.9 and the mean depression score was 7.36 ± 4.8 . Sixty (30%) patients had high anxiety and 93 (46.5%) patients had high depression scores. Among similar studies in the literature, Semiz et al.'s^[13] study of patients with AMI found anxiety in 24% of the patients and depression in 30%. In the study conducted by Kutlu et al.^[14] including patients in ICU, the highest rates of anxiety (37%) and depression (36.5%) were seen in MI among all diagnoses. In their study, Dias et al.^[15] found the rate of depression after AMI to be 41.6%. The results of some studies have shown that the rates of anxiety and depression are higher than our study. In their study with CAD patients, Ekici^[16] reported anxiety in 72.4% of the patients, while Özer et al.^[11] found anxiety in 100% of the patients and depression in 91.1% of AMI patients.

In the present study, while there was no significant difference in anxiety and depression scores according to sociodemographic characteristics such as sex, education and marital status, there was a significant difference between age and depression scores, and as age increased, depression scores increased. In their study, Aydemir et al.^[5] found that depression increased with age. Akkaya et al.^[17]

in their study, age was found to be an independent variable for depression in the multivariate regression analysis. It is thought that reasons such as decreasing expectations from life with age, increase in chronic diseases and their adverse effects on daily life, increase in uncertainties and losses would cause the level of depression to increase.

Being in the ICU is a stressful experience for patients. Psychological well-being is affected due to many factors such as the criticality of the patient's life, painful invasive interventions, inactivity, lack of privacy, disruption of sleep patterns, separation from loved ones and lack of adequate information. It is expected that patients' anxiety and depression levels would increase depending on the duration and frequency of exposure to these factors in ICU. In our study, a significant increase was observed in the patients' anxiety and depression scores as the length of stay in the ICU increased. Additionally, in the univariate regression analysis performed to identify independent predictors of ICU anxiety, the duration of ICU stay was found to be an independent predictor of anxiety. Similarly, in the study conducted by Eryiğit and Aydın,^[18] depression levels of patients increased, as the duration of stay in the ICU increased. The study by Bryant et al.^[19] showed that depression had a positive relationship with a longer stay in the ICU.

The symptoms experienced by AMI patients depending on their hemodynamic status and respiratory distress due to lung congestion in patients other than Killip Class I may cause fear of death and increase the development of anxiety in these patients. In particular, in patients with Killip Class III-IV, respiratory support and hemodynamic support may be required, and these factors may also predispose to the development of anxiety. In our study, with the influence of these possible factors, anxiety development was found to be significantly higher in patients other than Killip Class I. Additionally, being in Killip Class II-IV was found to be an independent predictor for anxiety by univariate and multivariate regression analysis. There is no study in the literature on the effect of the Killip class on the development of anxiety. Ekici^[16] investigated the relationship between CAD severity and anxiety levels and found that as the severity of CAD determined by Gensini and SYNTAX scores increased, anxiety scores as determined by HADS increased. However, Makca^[20] found no significant difference in anxiety and depression scores between

patients with non-critical coronary artery stenosis and critical coronary artery stenosis as evidenced by angiography findings.

In our study, we observed a negative significant relationship between the patients' calcium, total cholesterol, hemoglobin and hematocrit values and their depression scores, while there was a positive significant relationship between the troponin level and the depression scores. Ekici^[16] also found that there was a significant negative relationship between hemoglobin and hematocrit values and the HADS depression scale.

The main limitation to the present study is that the total number of patients and the number of those in Killip Class II-IV are relatively low. To support our study results, further larger-scale, prospective studies are needed regarding the predictive value of the Killip class in the development of anxiety in AMI patients.

In conclusion, Killip classification is an independent predictor of anxiety in AMI patients. Since patients with AMI, particularly those who are in Killip Class II-IV, are in the risk group for anxiety, it is of utmost importance to evaluate the anxiety status of these patients as soon as possible and to identify and reduce the affecting factors in order to facilitate adaptation to the disease and positively affect the treatment process.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea, design, data collection and writing the article: N.Ç.; Data analysis and literature review: N.Ş.; Design and data collection: S.G.; Data analysis and data collection: E.E.; Design, data collection and control: G.İ.A.; Idea, supervision and critical review: O.Ş.

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The role of systemic inflammatory response index to predict postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting

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ABSTRACT

Objectives: The aim of the present study was to investigate the association between systemic inflammatory response index (SIRI) and the occurrence of postoperative atrial fibrillation (POAF) in patients undergoing coronary artery bypass grafting (CABG).

Patients and methods: Between September 2022 and July 2024, a total of 276 consecutive patients (189 males, 87 females; mean age: 62.6 ± 7.3 ; range, 49 to 79 years) who underwent elective isolated CABG were included in this study. Clinical data and electrocardiograms of the patients were obtained. Based on the rhythm status during hospitalization after surgery, the patients were divided into two groups with POAF rhythm ($n=78$) and normal sinus rhythm ($n=198$). The SIRI index value was obtained based on the product of the number of neutrophils per monocyte divided by the lymphocyte count immediately before surgery.

Results: The mean value of preoperative SIRI in the group with POAF was 6.8 ± 1.1 , while it was 3.2 ± 0.8 in the non-POAF group, indicating a significant difference ($p=0.008$). According to the receiver operating characteristic (curve analysis, a SIRI higher than 5.5 could predict POAF with a sensitivity of 79.2% and a specificity of 66.8%. Along with increased SIRI, advanced age, history of hypertension and smoking, as well as reduced left ventricular ejection fraction were other predictors of POAF.

Conclusion: Assessing preoperative SIRI index can predict the occurrence of POAF in CABG patients with acceptable sensitivity and specificity values.

Keywords: Coronary artery bypass grafting, postoperative atrial fibrillation, systemic inflammatory response index.

New-onset postoperative atrial fibrillation (POAF) is a frequent sequel after coronary artery bypass grafting (CABG), with an overall prevalence ranged between 11 and 50%.^[1] The occurrence of this arrhythmic event is expected mostly during two to four days after operation.^[2] Patients with POAF are at an increased risk for complications after surgery including brain stroke, prolonged hospitalization, myocardial infarction as well as early or long-term death mainly due to the likelihood of thromboembolic events.^[3-5] The overall incidence of POAF has continued to rise, despite decades of attempts at therapeutic interventions.^[6] The main mechanisms of POAF remains unclear; however, some risk profiles including hypertension, history of heart failure, obesity, and advanced age have been identified to be associated with this arrhythmia.^[7,8] Moreover, some cardiac-related changes such as atrial fibrosis and atrial dilatation have been shown to be related to the risk for POAF.^[9] Additionally, due to

the close association of cardiac arrhythmia with the activation of inflammatory cascades, evidence regarding the relationship between the occurrence of this event and the activity of inflammatory markers has become extremely strong.^[10]

The systemic inflammatory response index (SIRI) as the product of neutrophil count and monocyte count divided by lymphocyte count is currently identified as an applicable inflammatory index to describe the pathophysiological causes of many disorders with a strong inflammatory bed such

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as diabetes mellitus, rheumatological disturbances, metabolic disorders, cerebrovascular events, renal insufficiency and even cardiovascular disorders.^[11-13] Recently, the association of increased SIRI and the risk for cardiac arrhythmias has strengthened.^[14] From a pathophysiological perspective, as structural and electrophysiological properties in cardiac myocytes provide a meaningful response in the form of inflammatory responses to any pathological changes, a strong association of cardiac functional abnormalities including cardiac arrhythmia and systemic inflammatory responses is predictable. In this regard, the emergence of some anatomical and functional abnormal changes in heart tissue such as fibrosis, endothelial dysfunction, cellular apoptosis and even cardiac necrosis which are strongly associated with cardiac arrhythmias have a close link to inflammatory responses.^[15] However, whether the occurrence of systemic inflammatory responses, particularly the SIRI index, can be an indicator of the risk of atrial fibrillation (AF), is still unclear. Evidences in this regard have recently been presented. It has been found an association of raising the serum levels of inflammatory markers such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) with the risk for AF.^[16-18] Also, the association of SIRI with the risk for adverse outcomes following CABG has been also shown.^[20] However, the association between SIRI and the occurrence of POAF remains uncertain. In the present study, we aimed to investigate the association between SIRI and the occurrence of POAF in patients undergoing CABG.

PATIENTS AND METHODS

This single-center, cross-sectional study was conducted at Okan University Hospital, Department of Cardiovascular Surgery between September 2022 and July 2024. A total of 276 consecutive patients (189 males, 87 females, mean age: 62.6±7.3, range, 49 to 79 years) who underwent elective isolated CABG and whose clinical data and electrocardiogram data of the patients were reached included. Patients under 18 years of age, patients undergoing concomitant cardiac procedures, those with chronic underlying disorders such as liver or kidney disorders, patients with underlying inflammatory diseases, a history of thyroid disorders, a history of cancer, or patients with a history of corticosteroid treatment

within the past six months were excluded from the study. Written informed consent was obtained from each patient. The study protocol was approved by the Okan University Hospital Ethics Committee (date: February, 2022, no: TR.OK.REC.2025.121). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Based on the rhythm status during hospitalization after surgery, the patients were classified into two groups with POAF rhythm (n=78) and normal sinus rhythm (n=198). In this study, AF was defined as the presence of irregular RR intervals with the absence of discrete P waves complicated by fibrillatory waves. Also, new-onset AF (NOAF) was identified as the occurrence of an AF episode lasting at least 30 sec during the hospital stay.

Background data including demographic characteristics, clinical history, medication history, and laboratory findings were all extracted through a review of the patients' archived records. In this regard, the SIRI index value was obtained based on the product of the number of neutrophils per monocyte divided by the lymphocyte count. Finally, first, the mean of the index was compared between the two groups with and without POAF. Then, using a multivariate logistic regression model in the presence of confounding background factors, the difference in POAF between the two groups was re-evaluated. Then, based on the analysis of the area under the curve (AUC) of the receiver operating characteristics (ROC) curve, the value of POAF in distinguishing between the two rhythm states of POAF and sinus rhythm was determined, the most optimal cut-off value for POAF, and the sensitivity and specificity of this index in distinguishing POAF from sinus rhythm were evaluated.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The t-test was used to compare quantitative variables and the chi-square test was used to compare qualitative variables. The difference in SIRI between the groups with and without POAF was assessed by the multivariate linear regression model with the presence of baseline variables. The area under the ROC curve analysis was used to determine the

diagnostic value of the SIRI scoring system in predicting POAF. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 276 patients, 78 (28.2%) had POAF. Comparing baseline characteristics between the subgroups with and without POAF showed significantly higher mean age, as well as higher prevalence rates of hypertension and smoking in the group with POAF compared to the group with normal sinus rhythm (Table 1). With respect to cardiovascular parameters, those with POAF had significantly lower left ventricular ejection fraction (LVEF) on admission; however, no significant difference was revealed between the two groups in the number of coronary arteries involvement ($p>0.05$).

The mean value of preoperative SIRI in the group with POAF was 6.8 ± 1.1 , while it was 3.2 ± 0.8 in the non-POAF group, indicating a significant

difference ($p=0.008$). The multivariate linear regression model with the presence of baseline parameters showed a significant difference in SIRI between the groups with and without POAF ($\beta=0.382$, $p=0.002$) (Table 2). According to the ROC curve analysis, assessing the value of preoperative SIRI could effectively predict the occurrence of POAF (AUC=0.788, 95% confidence interval (CI): 0.603-0.973). The most optimal cut-off value of SIRI to predict POAF was 5.5, yielding a sensitivity of 79.2% and a specificity of 66.8% (Figure 1).

DISCUSSION

The cause of AF following major cardiac surgery is still unclear. However, based on available evidence, the role of activation of local and systemic inflammatory factors following surgical manipulation, as well as underlying dysfunction of the cardiac conduction system, is quite prominent.^[7-10] Overall, the available evidence supports the central role of immune remodeling in the development

Table 1
Comparing baseline characteristics between groups with and without POAF

	Group with POAF (n=78)			Group without POAF (n=198)			<i>p</i>
	n	%	Mean±SD	n	%	Mean±SD	
Sex							
Male	55	70.5		134	67.6		0.758
Mean age (year)			65.6±8.8			59.7±5.6	0.001
Mean BMI (kg/m ²)			27.4±1.5			26.6±1.2	0.223
History of hypertension (%)	44	56.4		56	28.3		0.001
History of diabetes (%)	22	28.2		44	22.2		0.656
History of hyperlipidemia (%)	17	21.8		41	20.7		0.779
Current smoking (%)	14	17.9		32	16.1		0.856
Preoperative LVEF (%)			48.6±6.2			53.4±7.8	0.024
Number of coronary arteries involved							0.835
One-vessel	6	7.7		15	7.6		
Two-vessel	22	28.2		61	30.8		
Three-vessel	50	64.1		122	61.6		
Using CPB (%)	49	62.8		122	61.6		0.779
CPB time (min)			96.6±35.3			95.0±33.6	0.079
Cross-clamp time (min)			78.2±28.4			77.2±32.2	0.275
The mean SIRI value			6.8±1.1			3.2±0.8	0.008

POAF: Postoperative atrial fibrillation; SD: Standard deviation; BMI: Body mass index; LVEF: Left ventricular ejection fraction; SIRI: Systemic inflammatory response index; CPB: Cardiopulmonary bypass.

Table 2				
Multivariate linear regression analysis to determine the difference in SIRI between the groups with and without POAF				
Items	Unstandardized coefficients		T score	Sig.
	Beta	SE		
Sex	0.395	0.402	0.982	0.335
Occurrence of POAF	0.382	0.113	3.387	0.002
Body mass index	0.014	0.087	0.166	0.869
Age	0.009	0.002	4.827	0.001
Hypertension	0.003	0.119	0.022	0.983
Diabetes mellitus	0.099	0.111	0.886	0.383
Hyperlipidemia	0.133	0.113	1.172	0.251
Smoking	-0.614	0.001	-0.735	0.468
Three-vessel disease	0.003	0.002	1.445	0.159
CPB	0.0001	0.001	-1.737	0.093
CPB time	-0.007	0.016	-0.427	0.672
Cross-clamp time	-0.107	0.183	-0.587	0.562
LVEF	0.053	0.130	0.409	0.686

SIRI: Systemic inflammatory response index; POAF: Postoperative atrial fibrillation; SE: Standard error; CPB: Cardiopulmonary bypass; LVEF: Left ventricular ejection fraction.

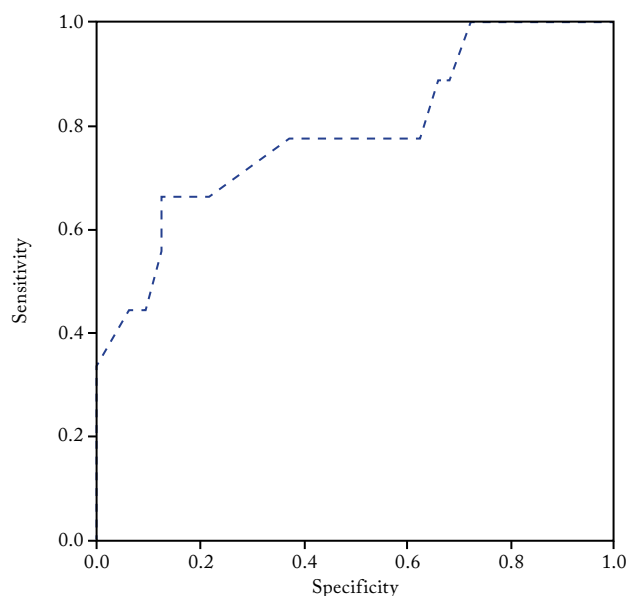


Figure 1. The area under the ROC curve indicates high value of SIRI to discriminate POAF from non-POAF groups (AUC=0.889).

ROC: Receiver operating characteristic; SIRI: Systemic inflammatory response index; POAF: Postoperative atrial fibrillation; AUC: Area under the curve.

of AF after surgery. Immune remodeling mainly refers to the impairment of atrial composition due to the activation of immune cells following cardiac manipulations.^[19] Indeed, immune remodeling flare alterations in structural and conductive systems of the atrium which may ultimately lead to atrial-related arrhythmias such as AF. In other words, any abnormal changes in heart architecture such as due to metabolic disturbances, heart failure, ischemic cardiac events and even following cardiac interventions can activate inflammatory factors such as neutrophils, proinflammatory biomarkers, platelets, lymphocytes, and macrophages which predispose the heart to abnormal cardiac remodeling and, thus, to arrhythmias including AF.^[20] In this regard, the activation of neutrophils and macrophages can result in production and secretion of some cytokines such as interleukin (IL)-1B, IL-6, IL-17A, and tumor necrosis factor-alpha (TNF- α) that may lead to appear atrial fibrosis, the main basis for the development of atrial arrhythmias. Based on the confirmed role of inflammatory factors in the development of AF and also considering the

prominent role of SIRI in the occurrence of cardiac arrhythmic disorders, currently the hypothesis of a relationship between the occurrence of AF and SIRI has gained great strength, particularly in the context of cardiac interventions.^[21,22] To illustrate, as indicated by Wang et al.,^[23] SIRI could effectively predict new-onset in patients with ST-segment elevation myocardial infarction following percutaneous coronary intervention. In another study, Hinoue et al.^[24] showed that preoperative SIRI was a useful prognostic biomarker for predicting POAF in patients undergoing cardiac surgery using cardiopulmonary bypass (CPB). Also, Luo et al.^[25] revealed that the increased SIRI could predict an increased risk of the POAF and independently predicted the late recurrence of AF after CryoMaze concomitant with mitral valve surgery. As shown in the present study, preoperative assessment of SIRI can be effective in predicting the occurrence of postoperative AF. In this context, values higher than 5.5 with acceptable sensitivity and specificity can be more likely to occur with this postoperative complication. Of note, it should be kept in mind that this cut-off value may vary greatly based on the underlying characteristics of the patients as well as the type of procedure performed.

As another finding of the study, and in line with previous studies, the main predictors of POAF occurrence, in addition to SIRI index, were old age, history of hypertension, and history of smoking. Other studies have also pointed to some background parameters, as well as procedure-related variables as predictors of this complication. In a study by Lotter et al.,^[26] advanced age, a P-wave duration of ≥ 100 ms, chronic obstructive pulmonary disease (hypertension <1 point>, age >75 years <1 point>, stroke or transient ischemic attack <2 points>, chronic obstructive pulmonary disease <1 point>, and heart failure <2 points> [HATCH]) score, and CPB time ≥ 100 min were associated with POAF. Erdolu and As^[27] also reported that higher age and increased atrial volume along with reduced LVEF were all associated with the risk for POAF. Apart from the role of underlying risk factors, intraoperative characteristics have also been suggested as significant factors associated with the occurrence of AF. In this context, although in the present study, we did not find a relationship between CPB or cross-clamp time, both factors have been identified in some studies as important and influential factors on the occurrence

of this arrhythmia. Overall, the occurrence of this complication can be considered the result of a multifactorial interaction between preoperative and intraoperative factors. Therefore, in addition to the role of inflammatory factors such as SIRI, special attention should be paid to preoperative factors and procedural parameters.

Nonetheless, there are some limitations to this study. First, the predictive value of SIRI was only evaluated in predicting the occurrence of postoperative atrial fibrillation, and the role of this marker in predicting the occurrence of long-term arrhythmias (through long-term follow-up of patients) was not evaluated. Second, the predictive value of SIRI was not compared with other inflammatory and proinflammatory factors. Finally, due to the possibility of differences in atrial fibrillation rates in different surgical techniques, the difference in the value of SIRI in predicting arrhythmias between off-pump and on-pump types was not compared.

In conclusion, POAF is a common postoperative complication after CABG which can be induced by the activation of different inflammatory processes. Therefore, the role of SIRI index to predict the occurrence of POAF is mostly highlighted in recent years. Our study results suggest that increased SIRI along with other parameters such as advanced age, history of hypertension, smoking and reduced LVEF can effectively predict POAF in CABG patients. Further large-scale, prospective studies are needed to draw more reliable conclusions on this subject.

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The effect of cardioplegia techniques on left ventricular functions in coronary artery bypass grafting: A comparison with tissue Doppler echocardiography

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ABSTRACT

Objectives: This study aims to evaluate the effects of antegrade cardioplegia (ACP) and combined antegrade/retrograde cardioplegia (ARCP) on left ventricular systolic and diastolic function in patients undergoing elective coronary artery bypass grafting (CABG) using tissue Doppler echocardiography (TDE).

Patients and methods: Between September 2010 and September 2012, a total of 40 patients (29 males, 11 females; mean age: 62±1.45 years; range, 27 to 78 years) who underwent elective isolated CABG under cardiopulmonary bypass were included. The patients were equally divided into two groups (n=20). Group 1: Antegrade cold blood cardioplegia (0-6°C), Group 2: Antegrade + retrograde cold blood cardioplegia (0-6°C). The TDE was performed preoperatively and was repeated at Weeks 1 and 4 postoperatively. Isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT), ejection time (ET), mitral annular waves, and diastolic velocity/myocardial E velocity (E/Em), late diastolic velocity (A) ratios were measured using TDE. The Tei index was calculated to assess the global function.

Results: The transmitral (E), E/A ratio, ejection fraction (EF), IVRT, IVCT, and myocardial performance index (MPI) significantly increased, whereas the transmitral (A), E wave deceleration time (EDT), and ET decreased. In the ARCP group, (E), the E/A ratio, EF, IVRT, IVCT, and MPI increased and ET decreased; however, (A) and EDT did not change. Both groups showed an improvement in cardiac function after revascularization.

Conclusion: Our study results show that both ACP and ARCP yield similar outcomes on cardiac systolic, diastolic, conduction system, and left ventricular functions. Revascularization has positive effects on systolic, diastolic, left ventricular, and conduction system function, leading to a significant improvement in segmental systolic and diastolic functions of the heart in the first month postoperatively.

Keywords: Coronary artery bypass grafting, myocardial protection, tissue Doppler echocardiography.

For optimal myocardial protection, homogeneous distribution of the cardioplegic solution is critical. This is mostly dependent on the way cardioplegia is delivered. Each technique offers different advantages according to the individual patient and procedural characteristics. The most common use in practice is antegrade delivery of cardioplegia via the aortic root, as it is simple to perform and causes rapid diastolic cardiac arrest.^[1] However, several studies have suggested that combined cardioplegia offers distinct advantages over antegrade cardioplegia (ACP) in terms of preservation of myocardial function and reduction of ischemic injury.^[2] Assessment of myocardial function after coronary artery bypass grafting (CABG) is critical for

determining the efficacy and safety of cardioplegia strategies. Reperfusion after CABG is expected to improve left ventricular (LV) systolic and diastolic function and increase long-term survival.^[3] Wall motion abnormalities observed early after CABG are among the most important indicators of myocardial

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ischemia. This is because, during ischemia, significant changes in systolic and diastolic function occur both regionally and globally in the LV.^[4] By evaluating myocardial functional recovery in the early postoperative period, we attempt to contribute to a better understanding of the effects of myocardial conduction strategies on clinical outcomes and functional recovery and to guide the selection of cardioplegia strategies in clinical practice.

Tissue Doppler echocardiography (TDE) is an imaging modality which allows quantitative assessment of myocardial motion. It was first described in 1989.^[5] It uses early diastolic velocity (E), late diastolic velocity (A), E/A ratio, myocardial performance index (MPI), isovolumic relaxation time (IVRT), and isovolumic contraction time (IVCT) to analyze LV function. Unlike conventional echocardiography, it can provide more detailed information on regional myocardial systolic and diastolic functions based on detailed analysis of myocardial velocities.

Although many studies have examined LV function in the post-CABG period, early and late TDE studies are limited. In addition, existing studies have mostly focused on the changes in LV systolic function after CABG. However, LV diastolic dysfunction is directly related to perioperative outcomes in patients undergoing cardiac surgery.^[6,7]

Although ACP is a safe and effective method of myocardial protection, aortic regurgitation in the presence of severe coronary stenosis can result in an inhomogeneous, inadequate distribution. Therefore, myocardial areas distal to the lesion are poorly protected, resulting in myocardial injury and delayed functional recovery.^[8] Although the combined cardioplegia technique is widely used currently, the comparative effects of these techniques on LV function remain a matter of debate in cardiac surgery literature. This dual approach is hypothesized to enhance myocardial protection by providing comprehensive perfusion in all myocardial layers, even in patients with advanced coronary pathology.^[9] In the present study, we, therefore, aimed to objectively evaluate the effect of reperfusion provided by different cardioplegia strategies on myocardial systolic and diastolic performance in CABG and to reveal potential differences in the postoperative period.

PATIENTS AND METHODS

This single-center, prospective study was conducted at Bülent Ecevit University, Faculty of Medicine, Department of Cardiovascular Surgery between September 2010 and September 2012. A total of 40 patients (29 males, 11 females; mean age: 62±1.45 years; range, 27 to 78 years) who underwent elective isolated CABG under cardiopulmonary bypass (CPB) were included. Inclusion criteria were as follows: (i) 18-80 years of age, (ii) Elective, isolated coronary bypass surgery. Exclusion criteria were as follows: (i) Congenital or acquired valve disease, (ii) Hypertrophic, restrictive or dilate cardiomyopathy, (iii) History of atrial fibrillation or ventricular arrhythmia, (iv) QRS duration >120 ms, (v) Pulmonary hypertension, ventricular aneurysm or valvular/congenital heart disease, (vi) Non coronary artery bypass surgery, (vii) Redo coronary artery bypass surgery, (viii) Need for urgent surgery, (ix) Cases where postoperative intra-aortic balloon is used or complications develop, (x) Patients with EF<30. To ensure homogeneity in the study and minimize possible biases, the patients were divided into two equal groups (n=20) using a computer-assisted random assignment method: Group 1: those who received ACP only and Group 2: those who received a combination of antegrade/retrograde cardioplegia (ARCP). Randomization was independently performed using the cardioplegia method. The study flowchart is shown in Figure 1. Written informed consent was obtained from each patient. The study protocol was approved by the Bülent Ecevit University Health Sciences Research Ethics Committee (date: 20.06.2010, no: 2010/17). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients underwent a standard general anesthesia protocol for CABG. All surgical procedures were performed by three experienced surgeons working in the same center according to standard protocols. There were no technical differences between the surgeons. After median sternotomy, the left internal mammary artery (LIMA) was prepared and anticoagulated with heparin (300 U/kg). Cannulation was performed from the aorta and right atrium. A roll pump (Jostra Lund, Sweden) and membrane oxygenator (Compactflo Evo, Dideco, Italy) were used for CPB. Rectal temperature was maintained between 32 and 33°C

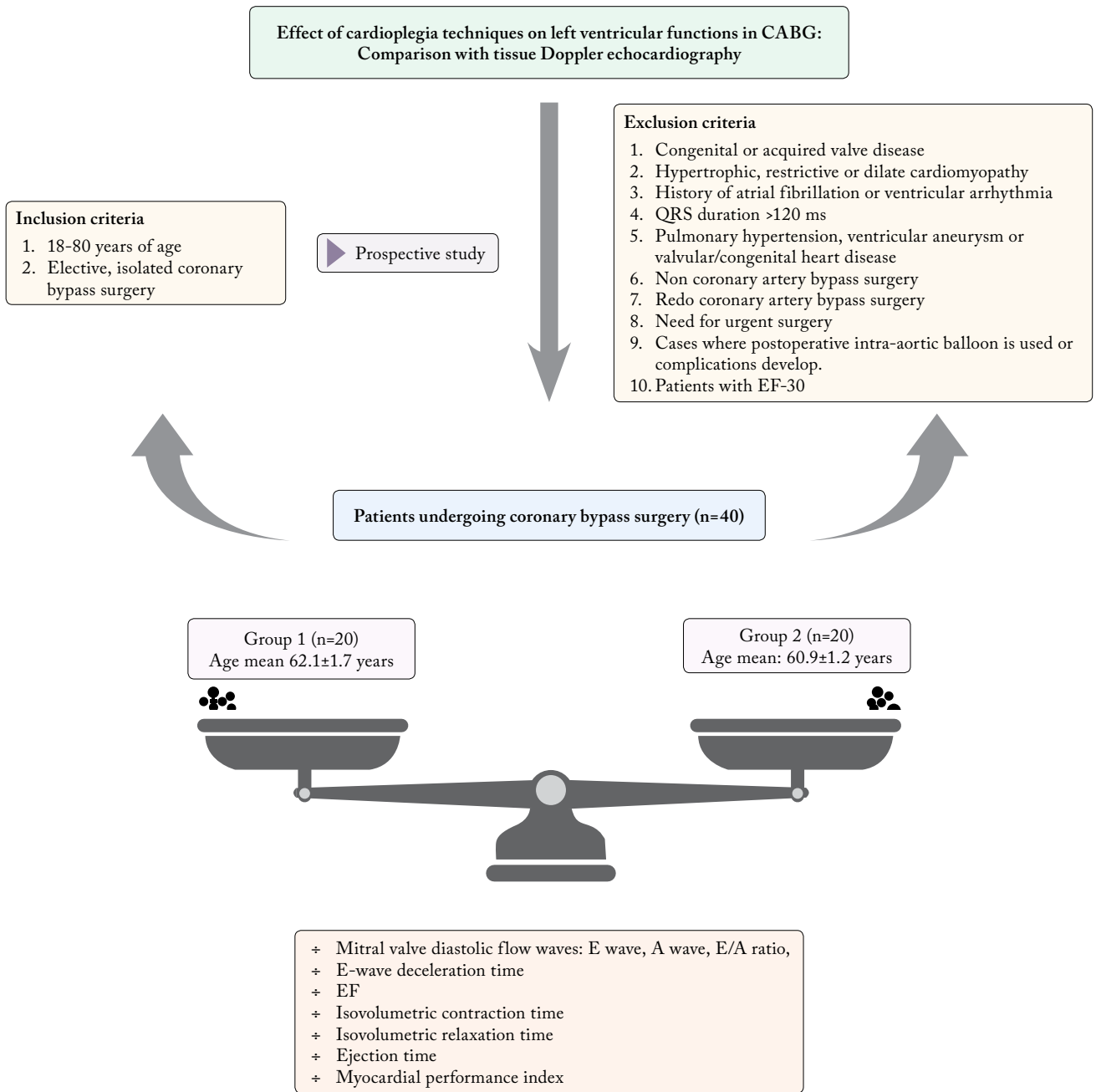


Figure 1. Study flowchart.

CABG: Coronary artery bypass grafting; QRS: QRS complex; E: Transmitral early diastolic velocity; A: Transmitral late diastolic velocity; EF: Ejection fraction.

throughout the operation. For myocardial protection, systemic moderate hypothermia (30 to 33°C) was maintained and cold blood cardioplegia (0 to 6°C) was administered. The ACP was administered at a flow rate of 250 to 350 mL/min, under a line pressure of 150 to 200 mmHg, at a mean dose of 15 to 20 mL/kg.

The ARCP was administered with $\frac{2}{3}$ of the total cardioplegia delivered antegrade and $\frac{1}{3}$ retrograde. Retrograde cardioplegia was administered at a flow rate of 200-250 mL/min with a coronary sinus pressure of 30-40 mmHg. The cardioplegia solution was blood-based and contained potassium chloride,

magnesium sulfate, and lidocaine. Warm blood cardioplegia (36°C) was induced after CPB. After the completion of surgery, heparin was neutralized with protamine hydrochloride at a 1:1 to 1.3 ratio. Following CPB, the heart was started spontaneously or by defibrillation, and CPB was terminated after hemodynamic stability was achieved. The LIMA and left anterior descending artery (LAD) anastomosis was performed in all the patients, and complete revascularization was achieved.

A 12-lead surface electrocardiogram (ECG) was obtained from all patients. Heart rate, R-R interval, QRS and QT intervals were measured manually, and the QT interval was corrected with Bazett's formula ($QT_c = QT/\sqrt{R-R}$).

Time points of Weeks 1 and 4 were selected for TDE. In the first week measurement, myocardial function changes in the early postoperative period due to ischemia-reperfusion were observed.^[9,10] In the fourth week measurement, the mid-term myocardial recovery process was evaluated. In previous studies in literature, Week 4 is recommended as an optimal time frame for early myocardial recovery.^[11,12] Echocardiography was performed using the General Electric Vivid Five (GE Vingmed Ultrasound AS, Horten, Norway) device. Two-dimensional (2D) images were obtained from standard parasternal long and short axes and apical four- and two-space slices. Left ventricular ejection fraction (EF) was calculated using the modified Simpson method. Using TDE, the mitral annular waves (myocardial E velocity [Em], myocardial A velocity [Am], and mitral peak systolic velocity [Sm]), E/Em ratios, IVCT, isovolumetric relaxation time IVRT, and ejection

time (ET) were measured. All TDE measurements were performed by an experienced cardiologist with a single rater to avoid interobserver variability. Measurements were performed using the blinded observer method.

Statistical analysis

Statistical analysis was performed using the PASW version 18.0 software (SPSS Inc., Chicago, IL, USA). Continuous data were expressed in mean \pm standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. The distribution of quantitative variables was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. An independent sample t-test was applied for independent quantitative variables with a normal distribution, while the Mann-Whitney U test was applied for independent quantitative variables without a normal distribution. The chi-square test or Fisher exact test was used to compare categorical variables. For repeated measures, one-way analysis of variance (ANOVA) was used for normally distributed data, and Friedman's test was used for non-normally distributed data. A *p* value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Of a total of 40 patients included in the study, there were 20 patients in Group 1 and 20 patients in Group 2. There was no significant difference in the mean age between the groups (*p*=0.666). The clinical characteristics of the patients are summarized in Table 1.

	Group 1 (n=20)			Group 2 (n=20)			<i>p</i>
	n	%	Mean \pm SD	n	%	Mean \pm SD	
Age (year)			62.1 \pm 1.7			60.9 \pm 1.2	0.912
Sex							0.808
Female	3	15		8	40		
Male	17	85		12	60		
Hypertension	6	30		6	30		0.098
Diabetes mellitus	8	40.0		14	70.0		0.476
Hypercholesterolemia	9	45.0		12	60.0		0.421

SD: Standard deviation.

Table 2
Comparative analysis of tissue Doppler echocardiographic parameters before and after coronary artery bypass grafting in patients undergoing antegrade cardioplegia

	Preoperative	Postoperative 1 st week	Postoperative 1 st month	<i>p</i>
	Mean±SD	Mean±SD	Mean±SD	
E (mm/s)	0.70±0.03	0.70±0.03	0.80±0.02	0.035
A (mm/s)	0.88±0.03	0.85±0.05	0.92±0.04	0.025
E/A	0.83±0.05	0.85±0.03	0.90±0.02	0.022
EDT (s)	244.2±9.81	234.4±9.14	214.3±7.78	0.041
IVRT (s)	103.1±3.91	105.2±4.02	109.00±3.71	0.034
IVCT (s)	64.8±2.11	69.3±2.09	72.1±2.10	0.038
ET (s)	239.3±5.92	242.5±5.99	224.0±5.26	0.027
MPI	0.71±0.03	0.73±0.03	0.82±0.02	0.033
EF	57.60±1.62	58.85±1.64	62.00±1.34	0.018

SD: Standard deviation; E: Transmitral early diastolic velocity; A: Transmitral late diastolic velocity; EDT: E Wave deceleration time; IVRT: Isovolumic relaxation time; IVCT: Isovolumic contraction time; ET: Ejection time; MPI: Myocardial performance index; EF: Ejection fraction.

A statistically significant increase was found in transmitral (E), E/A ratio, EF, IVRT, IVCT, and MPI values ($p<0.005$), whereas a statistically significant decrease was observed in transmitral (A), E wave deceleration time (EDT), and ET ($p<0.005$) (Table 2).

As shown in Table 2, there was a statistically significant increase in the transmitral (E), E/A ratio, EF, IVRT, IVCT, and MPI ($p<0.005$). A statistically significant decrease was observed in

transmitral (A), EDT, and ET measurements ($p<0.005$).

Table 3 shows that there was a statistically significant increase in (E), E/A ratio, IVRT, ICT, EF, and MPI values in the TDE measurements performed preoperatively and on postoperative Days 7 and 30 in the ARCP group ($p<0.005$). A statistically significant decrease was also observed in the ET values ($p<0.05$). No significant changes were observed in A and EDT values ($p>0.05$).

Table 3
Comparison of tissue Doppler echocardiography parameters before and after coronary artery bypass grafting in patients with combined antegrade and retrograde cardioplegia

	Preoperative	Postoperative 1 st week	Postoperative 1 st month	<i>p</i>
	Mean±SD	Mean±SD	Mean±SD	
E (mm/s)	0.67±0.03	0.67±0.03	0.76±0.02	0.042
A (mm/s)	0.83±0.05	0.80±0.05	0.84±0.03	0.472
E/A	0.83±0.05	0.85±0.05	0.92±0.04	0.018
EDT (s)	244.2±9.81	234.4±9.14	214.03±7.78	0.182
IVRT (s)	103.1±3.92	105.2±4.02	109.0±3.70	0.028
IVCT (s)	64.80±2.10	69.35±2.09	72.10±2.10	0.032
ET (s)	239.30±5.91	242.55±5.99	224.05±5.26	0.024
MPI	0.71±0.03	0.73±0.03	0.83±0.02	0.028
EF	57.60±1.62	58.85±1.64	62.00±1.34	0.019

SD: Standard deviation; E: Transmitral early diastolic velocity; A: Transmitral late diastolic velocity; EDT: E Wave Deceleration time; IVRT: Isovolumic relaxation time; IVCT: Isovolumic contraction time; ET: Ejection time; MPI: Myocardial performance index; EF: Ejection fraction.

Table 4
Comparison of tissue Doppler segmentary region parameters before and after coronary artery bypass grafting in patients with antegrade cardioplegia

	Preoperative	Postoperative 1 st week	Postoperative 1 st month	<i>p</i>
	Mean±SD	Mean±SD	Mean±SD	
Basal septum				
Em (cm/s)	5.95±0.23	5.00±0.23	4.96±0.24	0.165
Am (cm/s)	8.54±0.43	8.70±0.43	8.70±0.42	0.352
S (cm/s)	6.30±0.25	6.09±0.27	6.09±0.27	0.047
Em/Am	0.72±0.44	0.60±0.41	0.60±0.41	0.037
Septal annulus				
Em (cm/s)	6.36±0.30	6.03±0.32	6.04±0.32	0.154
Am (cm/s)	8.01±0.34	8.18±0.32	8.16±0.31	0.546
S (cm/s)	6.24±0.32	6.22±0.28	6.23±0.28	0.618
Em/Am	0.82±0.50	0.76±0.55	0.77±0.55	0.123
Basal lateral				
Em (cm/s)	6.38±0.38	5.91±0.44	5.95±0.43	0.026
Am (cm/s)	7.73±0.56	7.68±0.54	7.67±0.55	0.873
S (cm/s)	6.06±0.38	6.01±0.44	6.06±0.38	0.765
Em/Am	0.92±0.10	0.84±0.10	0.88±0.10	0.265
Lateral annulus				
Em (cm/s)	6.60±0.48	6.30±0.57	6.27±0.55	0.004
Am (cm/s)	7.95±0.50	8.39±0.55	8.42±0.53	0.062
S (cm/s)	6.75±0.33	6.72±0.40	6.70±0.40	0.903
Em/Am	0.86±0.06	0.79±0.08	0.78±0.07	0.015

SD: Standard deviation; Em: Myocardial E velocity; Am: Myocardial A velocity; S: Mitral peak systolic velocity.

In the segmental regional analysis of ACP patients using TDE, pre- and postoperative myocardial Em, Am, Sm waves, and Em/Am values were measured, and measurements were taken from four different regions: basal and annulus of the septum and lateral wall. A significant decrease was observed in the postoperative Em value of the basal septum ($p=0.001$). There was no significant difference between the postoperative Day 7 and 30. A slight increase in Am was observed; however, this difference was not statistically significant ($p=0.540$). A statistically significant decrease was also observed in Em/Am values during the postoperative period ($p=0.01$). No significant changes were observed in the Sm values ($p=0.280$). These changes were similar in all measured regions of the myocardial wall (basal and annulus of

the septum, and basal and annulus of the lateral septum) (Table 4).

As shown in Table 5, a statistically significant decrease was observed in the Em/Am values for the basal septum in the postoperative period in the segmental analysis performed with TDE in Group 2 ($p=0.037$). Changes over time were not significant for any of the septal annulus measurements. A statistically significant decrease in Em values was observed in measurements taken from the basal septum and annulus of the lateral septum in the postoperative period ($p=0.026$ and $p=0.004$, respectively). The change in Am value was not significant in either segment. The Em/Am values were significantly lower in the postoperative period ($p=0.015$). In all analyzed TDE segments, the measurement values obtained between Days 7 and 30

Table 5				
Comparison of tissue Doppler parameters before and after coronary artery bypass grafting in patients with combined antegrade and retrograde cardioplegia				
	Preoperative	Postoperative 1 st week	Postoperative 1 st month	<i>p</i>
	Mean±SD	Mean±SD	Mean±SD	
Basal septum				
Em (cm/s)	5.46±0.32	5.15±0.38	5.15±0.37	0.165
Am (cm/s)	7.26±0.39	7.59±0.36	7.57±0.35	0.352
S (cm/s)	5.61±0.30	5.87±0.24	5.89±0.24	0.047
Em/Am	0.82±0.85	0.73±0.77	0.73±0.78	0.037
Septal annulus				
Em (cm/s)	6.79±0.33	5.63±0.20	5.65±0.20	0.031
Am (cm/s)	9.21±0.33	9.50±0.34	9.51±0.34	0.163
S (cm/s)	6.92±0.32	6.76±0.23	6.69±0.23	0.394
Em/Am	0.75±0.44	0.61±0.32	0.61±0.33	0.024
Basal lateral				
Em (cm/s)	5.68±0.32	5.08±0.36	5.13±0.36	0.003
Am (cm/s)	7.56±0.38	8.76±0.60	8.83±0.59	0.018
S (cm/s)	5.59±0.33	5.76±0.33	5.60±0.33	0.051
Em/Am	0.76±0.06	0.63±0.05	0.60±0.05	0.006
Lateral annulus				
Em (cm/s)	6.73±0.44	6.07±0.36	6.06±0.35	0.019
Am (cm/s)	9.14±0.41	9.63±0.42	9.60±0.43	0.226
S (cm/s)	7.32±0.42	7.30±0.43	7.28±0.45	0.891
Em/Am	0.76±0.06	0.65±0.05	0.65±0.05	0.009

SD: Standard deviation; Em: Myocardial E velocity; Am: Myocardial A velocity; S: Mitral peak systolic velocity.

Table 6				
Comparison of QRS and QTC values on ECG before and after CABG depending on the method of cardioplegia administration				
Cardioplegia method	Preoperative	Postoperative 1 st week	Postoperative 1 st month	<i>p</i>
	Mean±SD	Mean±SD	Mean±SD	
Antegrade cardioplegia				
QTC (ms)	413.5±4.42	423.95±4.68	414.35±6.40	0.086
QRS (ms)	90.15±3.04	91.50±3.26	87.95±3.59	0.335
Antegrad/retrograd cardioplegia				
QTC (ms)	410.5±6.50	414.35±6.40	413.50±6.48	0.143
QRS (ms)	85.90±3.85	87.95±3.59	86.60±3.72	0.835

SD: Standard deviation; QRS: QRS complex; QTc: Corrected QT interval; ECG: Electrocardiogram; CABG: Coronary artery bypass grafting.

in the postoperative period were not statistically different.

Comparison of the pre- and postoperative Week 1 and 4 TDE measurements revealed no statistically significant differences in the E, A, E/A

ratio, ET, EF, and MPI values between the groups ($p>0.05$).

Depending on the method of cardioplegia administration, the QRS and QTC values on ECG were compared before CABG and on

Days 7 and 30. The change in these values over time was not statistically significant in either patient group ($p > 0.05$) (Table 6).

DISCUSSION

Myocardial protection methods used during cardiac surgery directly affect surgical success and postoperative myocardial function. Diastolic dysfunction is one of the earliest signs of myocardial ischemia. In coronary artery disease, diastolic function deteriorates or improves before systolic function does.^[6] In ischemic heart disease, decreased E wave and E/A ratio, which indicate diastolic dysfunction in ischemic myocardial segments with TDE, and prolonged IVRT and EDT parameters have been reported.^[13]

In this study, significant increases in the early diastolic flow velocity (E), E/A ratio, and EF values were observed on postoperative Day 30, whereas decreases in the (A) and ET values were found in the ACP group, which is consistent with the literature. These findings suggest that a certain time period is required for the regulation of myocardial function. Increases in EF, E/A ratio, and (E) wave on postoperative Day 30 indicated that ventricular relaxation recovered after surgery, and systolic and diastolic functions tended to improve. A decrease in the (A) wave indicates a decrease in active atrial filling and an increase in the relaxation capacity of the ventricle, leading to passive filling.^[14] The decrease in ET may be associated with revascularization after CABG, optimization of myocardial contraction time, and more efficient filling dynamics due to the reduction in ischemic regions. In contrast, a statistically significant increase in the E value on postoperative Day 30 was observed in the combined cardioplegia group. However, the E/A ratio differed among the three time periods, and the postoperative Day 30 values were higher than the preoperative and postoperative Day 7 values. This periodic difference in our findings was interpreted to be compatible with data in the literature regarding early diastolic dysfunction in ischemic myocardial segments.^[14] In addition, in our study, the increases in time parameters, such as IVRT and IVCT, which were common in both cases, were evaluated as changes due to the short-term adaptation process of the myocardium. The effect of ACP on

diastolic improvement is similarly emphasized in the literature.^[15]

When TDE segmental myocardial analyses of both groups were performed, the Em and Am values in the ACP group mostly showed no significant postoperative change, whereas the Em/Am ratios decreased in all segments. This decrease was statistically significant for both basal and lateral walls. In the ARCP group, there was a significant decrease in the Em/Am ratio in all the segments. This suggests that the effects of cardioplegia may differ depending on the myocardial region, and that combined cardioplegia administration may produce more specific effects at the segmental level.^[15] In addition, the segmental myocardial velocity differences observed in both groups were considered to be indicators of myocardial fibrosis or ischemia in the early postoperative period. However, the stabilization of these values at follow-up suggests that this process is reversible and that both cardioplegia methods preserve myocardial function.

However, studies have demonstrated that right ventricular recovery can be achieved more effectively with combined cardioplegia and that it is superior in terms of postoperative inotrope use and the need for mechanical support.^[16] These findings may explain the myocardial segmental differences between the two cardioplegia methods used in our study.

The MPI is a global indicator of LV systolic and diastolic dysfunctions. An increase in MPI is important for assessing global cardiac function and myocardial recovery after CABG. In our study, significant increases in the postoperative MPI and EF values indicated that both methods supported myocardial function. However, this increase was more pronounced in Group 2. This finding suggests that combined cardioplegia may provide a more extensive and balanced myocardial protection.

In the literature, there are studies emphasizing the advantages of combined cardioplegia in providing more uniform, which found that the improvement in EF in the postoperative period was better with high-risk CABG.^[17] In our study, although there was no significant difference in EF values between the preoperative and early postoperative periods, the significant increase in the first postoperative month may be due to adaptive changes in the hibernating myocardium after revascularization. Simultaneously, surgery-induced inflammation and

myocardial edema in the early postoperative period after CABG may have had transient adverse effects on LV function. Medical therapies administered in the postoperative period, such as beta-blockers,^[18] angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs),^[19] may contribute to the improvement of LV function by reducing the load on the myocardium.

The similar QTc and QRS durations on preoperative and postoperative ECG in both groups suggest that the effects of cardioplegia methods on myocardial electrical stability were minimal. It has been reported in the literature that cardioplegia-induced hyperkalemia may cause the prolongation of QTc duration.^[20] In addition, QTc prolongation due to prolonged operation times has been reported in some studies.^[21] The non-significant prolongation of QTc duration observed in our study may be due to cardioplegia-induced hyperkalemia or prolonged surgery, similar to the findings of previous studies.

In the current study, similar results were found in the myocardial recovery processes in the first month after CABG using both the methods. However, it is frequently reported that combined cardioplegia provides significant advantages in terms of myocardial protection compared with ACP.^[16] Therefore, it is emphasized that it may be a more favorable option, particularly in patients with complex coronary artery disease,^[22] hypertrophic myocardial tissue,^[23] redo-CABG,^[24] and high-risk patients with low preoperative EF.^[17] Taken together, each method has its advantages and disadvantages. Therefore, the cardioplegia strategy should be individualized based on the clinical characteristics of the patient and experience of the surgeon. In the future, prospective studies involving larger patient groups and the evaluation of long-term outcomes would make important contributions to the optimization of cardioplegia methods. Based on the findings of our study, cardioplegia strategies should be individualized on a patient-by-patient basis. In addition, TDE and other advanced imaging modalities should be used both in the decision-making process for preoperative myocardial protection techniques and in the establishment of myocardial rehabilitation and pharmacological support protocols in the early postoperative period.

Nonetheless, this study has some limitations. First, the relatively small number of patients and single-center design limit the generalizability of the results. Studies evaluating changes in myocardial function after CABG often require long-term follow-ups. However, our study focused on early postoperative myocardial recovery, and the first month results were evaluated in terms of the number of patients and follow-up period. Studies evaluating changes in myocardial function after CABG often require long-term follow-ups. However, our study focused on early postoperative myocardial recovery and evaluated the results in the first month in terms of the number of patients and the follow-up time. Considering that the myocardial healing process may take weeks, long-term results may have been underestimated. Furthermore, the correlation of regional strain parameters assessed by TDE with coronary stenosis was not analyzed. Furthermore, biomarkers such as troponin levels were not analyzed, which may provide additional information for evaluating the effectiveness of myocardial protection strategies. On the other hand, although TDE parameters were less affected by changes in LV preload and afterload compared to conventional Doppler parameters, inotropic, vasodilator and diuretic therapies initiated after CABG may have affected these parameters to some extent. The Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score, an important prognostic tool for assessing the anatomical complexity of coronary artery disease, was not used in this study. This limitation limits the generalizability of the results obtained, particularly for patients with complex coronary lesions. In our study, patients in both groups had similar demographic and clinical characteristics, and showed a homogeneous distribution in terms of preoperative EF, New York Heart Association (NYHA) functional class, LV diastolic function, and other hemodynamic parameters. However, the lack of consideration of more specific anatomical variables, such as the SYNTAX score, is a significant limitation. Further large-scale, long-term, prospective studies are warranted to confirm these findings.

In conclusion, both antegrade and combined cardioplegia techniques demonstrated equivalent early improvements in left ventricular function after CABG, supporting prior evidence on their myocardial protective efficacy.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceptualization, investigation, writing-original draft, data curation: M.Y.; Review, and editing, formal analysis, supervision: S.A.T.; Investigation, methodology, review and editing: T.K.; Methodology, writing-review and editing: E.U.

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Comparison of short- and mid-term outcomes of antiplatelet versus anticoagulant use in peripheral artery disease patients with synthetic grafts

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ABSTRACT

Objectives: This study aimed to compare the short- and mid-term outcomes of graft patency in patients receiving anticoagulant or antiplatelet therapy during the postoperative period.

Patients and methods: A total of 109 patients (103 males, 6 females; mean age 69.5±7.9 years; range 44 to 80 years) were included in this retrospectively study between January 2015 and January 2022. Of these, 46 patients were receiving anticoagulant therapy, while 63 were on antiplatelet therapy. The graft patency rates were evaluated during outpatient follow-ups at one-, three-, six-, and 12 months through physical examinations and imaging methods (Doppler ultrasonography or computed tomographic angiography).

Results: The efficacy of anticoagulant and antiplatelet therapy was similar after femoropopliteal bypass using a synthetic graft.

Conclusion: We believe that treatment plans should be individualized for each patient in the postoperative period.

Keywords: Antiagregan therapy, anticoagulant therapy, peripheral artery disease, synthetic graft usage.

Considering its past, present, and future, many unanswered questions remain regarding peripheral artery disease (PAD). Addressing some of these questions, particularly in the context of femoropopliteal occlusive artery disease, constitutes the main objective of our study. Peripheral artery disease is one of the major causes of morbidity that negatively affects patients' quality of life.^[1] Atherosclerosis is the primary cause of most lower extremity vascular issues. As a result of atherosclerosis, stenosis or narrowing occurs in the main arteries supplying the lower extremities, leading to symptoms in patients. In addition to atherosclerosis, PAD also includes thrombosis, arterial inflammation, arterial dilation, aneurysm formation, or external compression leading to arterial stenosis or occlusion.^[2,3]

The most common site for the development of atherosclerotic occlusive lesions in the lower extremities is the femoropopliteal artery segment. When occlusive disease occurs in these arteries, a wide range of clinical manifestations can arise, from claudication to amputation, depending on the severity of the

lesion. The severity of clinical symptoms in PAD is determined by the degree of arterial narrowing, the ability of collateral circulation to provide sufficient tissue perfusion, blood viscosity, and the presence of comorbid conditions in the patient.^[4]

Several classic cardiovascular risk factors, such as diabetes mellitus (DM), dyslipidemia, smoking, hypertension (HT), and advanced age, play a role in the etiology of PAD.^[2,3] The signs and symptoms of PAD reflect the degree of circulatory impairment, indicating whether this deterioration occurs gradually over a long period or acutely and irreversibly. Proper clinical assessment is critical for accurate diagnosis and for determining the most appropriate treatment strategy.

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After deciding on surgical intervention for PAD, two main treatment options are available: endovascular procedures and surgical intervention. The burden of calcification in femoropopliteal lesions has been proven to affect both the success of the procedure and the mid-term restenosis rate. Ketenciler et al.^[5] and Fanelli et al.^[6] reported that an increased cross-sectional calcification burden observed on computed tomography angiography, along with a longitudinal calcification burden observed on digital subtraction angiography, is associated with a progressive decline in clinical success. Moreover, this study demonstrated that the cross-sectional calcification burden was a stronger predictor of poor outcomes compared to the longitudinal calcification burden.

Additionally, the severity of ischemia in the patient, the need for revascularization, and the suitability for revascularization should be evaluated through objective tests. When planning treatment after an objective assessment, factors such as comorbidities, prior medical history, and the necessity of surgical treatment should be considered.^[7-9]

For symptomatic patients, single antiplatelet therapy is recommended, whereas dual antiplatelet therapy is suggested for patients undergoing percutaneous intervention. In patients undergoing surgical intervention, the choice between dual antiplatelet therapy or a combination of antiplatelet and anticoagulant therapy should be made based on graft patency and bleeding risk.^[10]

In this study, we aimed to determine the short and medium term results on graft patency in patients who received anticoagulant and antiaggregant treatment in the postoperative period and their advantages and disadvantages over each other.

PATIENTS AND METHODS

This single-center, retrospective, observational cross-sectional study included adult patients who underwent surgery using a synthetic graft due to PAD at the Eskişehir Osmangazi University Faculty of Medicine between January 2015 and January 2022. A total of 109 patients (103 males, 6 females; mean age 69.5 ± 7.9 years; range 44 to 80 years) were included in the study. All patients were symptomatic, presenting with complaints such as claudication, pain, difficulty

walking, and early fatigue. For patients scheduled for surgery, any ongoing antiplatelet and anticoagulant treatments were discontinued one week prior to the procedure, and low-molecular-weight heparin was administered at a therapeutic dose based on body weight. Patients' demographic data (age and sex) and general health information (HT, DM, atrial fibrillation [AF], hyperlipidemia, chronic kidney disease, coronary artery disease, and smoking status) were retrieved from the hospital database. Written informed consent was obtained from all participants. The study protocol was approved by Eskişehir Osmangazi University Faculty of Medicine Ethics Committee (date: 19.10.2023, no: 45425468-42). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Surgical technique

Under general anesthesia, incisions were made in the femoral and supragenicular medial tibial regions. Proximally, the common femoral artery was dissected and suspended. Through the incision in the supragenicular medial tibial region, the supragenicular popliteal artery was similarly dissected and suspended. Heparin was administered at a dose of 100 IU/kg.

An arteriotomy was performed on the popliteal artery. A synthetic graft of appropriate diameter was anastomosed end-to-side in a continuous manner to the popliteal artery. The graft was then tunneled through a subcutaneous passage and delivered to the femoral region. An arteriotomy was also performed on the common femoral artery, and the proximal end of the graft was anastomosed end-to-side in a continuous fashion. Adequate flow was observed in both the proximal and distal sections of the graft. After confirming hemostasis, the surgical layers were closed in an appropriate manner.

Postoperative period

All patients were monitored in an intensive care unit for 24 h postoperatively. During this period, heparin infusion was administered at a dose adjusted to body weight. On the first postoperative day, 46 patients were started on anticoagulant therapy, while 63 patients received antiplatelet therapy (acetylsalicylic acid [ASA] and clopidogrel).

Patient data were obtained from follow-up examinations and hospital record systems. After discharge, patients underwent physical examinations,

Doppler ultrasonography, and, when necessary, computed tomography angiography to assess graft patency and complications at one-, three-, six-, and 12-month follow-up visits.

Statistical analysis

Data were analyzed using SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as frequency, percentage, and mean \pm standard deviation (SD). Categorical data were analyzed using the chi-square test and Fisher exact test. A p-value <0.05 was considered statistically significant.

RESULTS

The most common systemic disease was HT, observed in 63 (57.7%) patients, followed by hyperlipidemia in 61 (55.9%) patients. Coronary artery disease was present in 53 (48.6%) patients, DM in 50 (45.8%), smoking in 46 (42.2%), chronic kidney disease in eight (7.3%), and AF in five (4.5%) patients. The demographic and clinical data of the study population are summarized in Table 1.

The postoperative outcomes of the patients are presented in Table 2. A total of five (4.5%) patients

Table 1
Demographic and clinical data of the study population

	Anticoagulant (n=46)		Antiaggregant (n=63)		<i>p</i>
	n	%	n	%	
Sex					
Male	45	97.8	58	92.1	0.398 ^a
Female	1	2.2	5	7.9	
Hypertension	29	63	34	54	0.34 ^b
Hyperlipidemia	25	54.3	36	57.1	0.77 ^b
Coronary artery disease	23	50	30	47.6	0.80 ^a
Smoker	20	43.5	26	41.3	0.81 ^a
Chronic kidney failure	4	8.7	4	6.3	0.71 ^a
Diabetes mellitus	17	37	33	52.4	0.11 ^b
Atrial fibrillation	5	8.7	0	0	0.12 ^c

a Fisher exact test; b Pearson Chi-square test; c Chi-square test.

Table 2
Operative and postoperative outcomes

	Anticoagulant		Antiaggregant		Total		<i>p</i>
	n	%	n	%	n	%	
Number of patients (postoperative period)	47	43.1	62	56.9	109		0.96 ^a
Postoperative early stage bleeding-hematoma (first 24 h)	2	4.2	3	4.8	5	4.5	0.64 ^b
1 st month patency	45	95.7	60	96.7	105	96.3	0.32 ^b
3 th month patency	44	93.6	59	95.1	103	94.4	0.50 ^a
6 th month patency	44	93.6	58	93.5	102	93.5	0.85 ^a
1 st year patency	43	91.4	56	90.3	99	90.8	0.36 ^b
Wound infection	4	8.7	8	12.7	12	11	0.36 ^b
Amputation	4	8.7	6	9.5	10	9.1	0.58 ^b

a Chi-square test; b Fisher exact test.

required revision due to early bleeding or hematoma within the first 24 h. Twelve (11%) patients experienced wound infections, and 10 (9.1%) patients required amputation of the lower extremity.

DISCUSSION

In this study, we analyzed patency and survival outcomes in the postoperative period for patients who underwent femoropopliteal bypass procedures due to PAD. According to the literature, PAD is more prevalent in males.^[10] Factors such as higher rates of smoking, elevated low-density lipoprotein levels, and reduced high-density lipoprotein levels in males are thought to contribute to this trend. Similarly, in our study, PAD was more frequently observed in males, consistent with previous findings. Among our patients undergoing femoropopliteal bypass with synthetic grafts, 94.5% were male, and 5.5% were female.

Studies by Selvin et al.^[11] and Menke et al.^[12] reported a higher prevalence of PAD in patients with chronic kidney disease. In our study, femoropopliteal bypass was performed in eight patients with chronic kidney disease. Another subgroup characterized by poor survival and graft patency outcomes was those with AF. Previous studies have demonstrated a strong association between AF and major cardiac events, morbidity, and mortality.^[13] Among the five AF patients in our study, one required amputation, and another underwent reoperation due to graft thrombosis.

Amputation is a critical endpoint in the postoperative period following femoropopliteal bypass surgery for PAD. In a study conducted by Rahman and Özkısacık,^[14] the amputation rate was reported as 7.6%. Similarly, our study identified an amputation rate of 9.1%, aligning with the literature. Regarding antithrombotic therapy in patients undergoing femoropopliteal bypass with synthetic grafts, different treatment modalities have been reported in the literature.^[15] Additionally, various surgical clinics apply different treatment protocols, and optimization of these therapies remains an ongoing area of research. A meta-analysis of 16 studies evaluated the effect of antiplatelet therapy after femoropopliteal bypass.^[16] The analysis revealed that antiplatelet therapy with ASA or a combination of ASA and dipyridamole generally yielded positive effects on primary vessel patency rates after 12 months. Subgroup analysis suggested that

antiplatelet therapy might provide greater benefits in patients with synthetic grafts compared to those with vein grafts.^[16] A study comparing ASA plus placebo with ASA plus clopidogrel found that the latter combination did not increase overall efficacy in the peripheral bypass population but demonstrated statistically significant benefits in patients with prosthetic grafts.^[17] Furthermore, combined therapy was not associated with an increased bleeding risk.

In our study, based on previous findings, we administered dual antiplatelet therapy with ASA and clopidogrel in the postoperative period. In the follow-up of patients receiving dual antiplatelet therapy in this group beyond the first 24 h postoperatively, no major bleeding was observed. The majority of studies, as highlighted above, have focused on ASA and clopidogrel. However, there is insufficient data regarding the use of other antiplatelet agents in patients with synthetic grafts, emphasizing the need for further extensive studies.

The use of ASA, vitamin K antagonists (VKAs), and dual antiplatelet therapy after lower extremity bypass surgery was compared,^[15] and ASA use significantly improved graft patency compared to placebo. While VKAs did not affect graft patency rates, they were associated with approximately a two-fold increase in bleeding complications. Similar to the literature, our study found no significant difference in graft patency rates between the anticoagulant and antiplatelet groups (one-year patency rates of 84.8% for the anticoagulant group and 93.7% for the antiplatelet group).

The most common anticoagulation protocol in Türkiye involves initiating therapy with low-molecular-weight heparin and VKA, followed by transitioning to VKA monotherapy once the target international normalized ratio (INR) level of 2 is achieved and maintained for 24 h. However, Sargin et al.^[18] reported that patients spent only 34.3% of their follow-up time within the therapeutic INR range of 2 to 3. Moreover, the mean INR value remained below 2 in 52.03% of patients.^[18]

The multicenter prospective Bypass Oral Anticoagulants or Aspirin study randomized patients undergoing lower extremity bypass surgery to receive either anticoagulant therapy or antiplatelet therapy (ASA 80 mg/day).^[19] While overall graft patency rates did not differ significantly, subgroup analysis indicated that oral

anticoagulant therapy might improve venous graft patency rates compared to ASA, whereas ASA was more effective in improving synthetic graft patency compared to anticoagulants.^[19] These findings underscore the importance of medication-related health considerations, particularly in the elderly population.^[20] In our clinical follow-up, achieving and maintaining target INR levels remained a significant challenge in the anticoagulant group. Among our patients, 10 required rehospitalization due to elevated INR levels, yet no major bleeding events were detected. The low socioeconomic and awareness levels of our patients were identified as key factors influencing their adherence. Therefore, we believe that patients prescribed warfarin, as well as their caregivers, should receive comprehensive education on the importance of regular INR monitoring and its dietary and drug interactions.

This study had certain limitations. First, patency rates were assessed using Doppler ultrasonography in the postoperative period, which is more subjective and operator-dependent compared to computed tomography angiography. Second, the relatively small sample size was another limitation.

In conclusion, our findings indicate that short- and mid-term graft patency rates were comparable across both treatment groups. Consequently, we emphasize the necessity of considering patient demographics, procedural specifics, and adherence to treatment regimens when initiating postoperative medical management.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, data collection and/or processing: M.Ç.; Design, analysis and/or interpretation, literature review, writing the article, references and fundings, control/supervision, critical review: M.Ç., A.Ş.

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Impact of balloon inflation duration on angiographic outcomes in infrainguinal atherosclerotic lesions

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ABSTRACT

Objectives: This study aimed to evaluate the effect of short versus prolonged balloon inflation times on the degree of residual stenosis following peripheral balloon angioplasty.

Patients and methods: In this retrospective cohort study, 239 balloon angioplasty procedures performed on 192 patients (158 males, 34 females; mean age: 66±9.7 years; range, 42 to 94 years) between April 1, 2020, and September 1, 2020, were analyzed. Patients were categorized into two groups based on balloon inflation time: ≤1 min (n=138) and >2 min (n=101). Preoperative and postoperative angiographic images were compared to assess the degree of stenosis.

Results: No statistically significant differences were observed between the groups in terms of age or comorbid conditions (hypertension, diabetes mellitus, coronary artery disease, chronic renal failure, hyperlipidemia, and obesity; p>0.05 for all). Preoperative stenosis levels were similar between groups (p=0.738); however, residual stenosis was significantly lower in the prolonged inflation group (p<0.001). The incidence of arterial dissection was also reduced in this group. No significant differences were found between the groups regarding thrombosis or vascular perforation.

Conclusion: This study demonstrated that balloon inflation times exceeding 2 min reduced residual stenosis and complications such as dissection.

Keywords: Angioplasty, balloon inflation time, drug-eluting balloon, peripheral artery disease, residual stenosis.

Percutaneous transluminal angioplasty (PTA) is an established minimally invasive treatment for peripheral artery disease (PAD).^[1] While peripheral bypass surgery is reserved for select cases of advanced atherosclerotic disease, angioplasty is commonly preferred as the first-line intervention due to its lower invasiveness and faster recovery time.^[2]

The main objective of angioplasty is to mechanically dilate the vessel lumen by remodeling and compressing the atherosclerotic plaque. In recent years, drug-coated balloons have been introduced to improve clinical outcomes in PAD, drawing from experience in coronary interventions.^[3] These drug-coated balloons deliver antiproliferative agents, such as paclitaxel, directly to the vessel wall, minimizing the risk of restenosis without requiring a permanent vascular implant.^[4,5] Paclitaxel inhibits vascular smooth muscle cell proliferation and migration by inducing cell cycle arrest and apoptosis, thus preventing neointimal hyperplasia.^[6]

While numerous strategies have been proposed to reduce restenosis rates after angioplasty, many have not been rigorously evaluated in randomized clinical trials. One such procedural factor is balloon inflation time. Prolonged inflation may reduce dissection and vasospasm by inducing transient smooth muscle dysfunction, potentially resulting in less residual stenosis.^[7]

This study aimed to compare the immediate angiographic outcomes of two different balloon

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inflation durations, short (≤ 1 min) and prolonged (> 2 min), in patients undergoing infrainguinal balloon angioplasty for PAD.

PATIENTS AND METHODS

This retrospective single-center study was conducted on 401 patients who underwent peripheral angiography between April 1, 2020, and September 1, 2020. Patients undergoing endovascular revascularization were identified using the guidelines of the European Society of Cardiology, American College of Cardiology/American Heart Association, and European Society for Vascular Surgery and national guidelines for the management of PAD.^[5,8-10] Data were retrospectively collected from patients' electronic medical records in a standardized form that included demographic and clinical characteristics and radiologic images (computed tomography angiography, as well as preoperative and postoperative angiography images). Adults (aged 18 years or older) who underwent angioplasty for infrainguinal atherosclerotic vascular disease (nonobstructive) were enrolled in the study. Exclusion criteria were suprainguinal occlusions, previous surgery for peripheral arterial disease, last peripheral balloon angioplasties at the same site, iliac arterial lesions, failed interventions, and venous interventions. Angioplasty was performed in both legs in 47 patients. A total of 192 patients (158 males, 34 females; mean age: 66 ± 9.7 years; range, 42 to 94 years) with 239 consecutive balloon angioplasties were included in the study. Written informed consent was obtained from all participants. The study protocol was approved by the Bakırçay University School of Medicine Ethics Committee (Date: 12.10.2020, No: 81/51). The study was conducted in accordance with the principles of the Declaration of Helsinki.

There were two surgical procedures in which two different balloon inflation times were used in the study. In one of the two procedures, the balloon inflation time was ≤ 1 min; in the other, it was > 2 min. Lesions of the superficial femoral artery, popliteal artery, and infrapopliteal artery were intervened. Balloon angioplasties were classified into two groups to compare balloon inflation times: 138 balloon angioplasties were performed for ≤ 1 min, and 101 procedures for > 2 min. Waiting times after the

nominal pressure was reached were evaluated. Carotid stenosis was measured according to a previous formula described in the North American Symptomatic Carotid Endarterectomy Trial and adapted for patients with PAD. Preoperative and postoperative angiographic images were compared to determine the degree of stenosis. The narrowest diameter observed in any plane of the lumen and the proportion of normal segment diameter in the proximal or distal part of that segment were calculated according to the following formula: (% stenosis = $[1 - (\text{minimal residual lumen diameter} / \text{distal or proximal normal lumen diameter})] \times 100$).^[11]

Residual stenosis was assessed immediately after angioplasty with a postoperative angiogram. After angioplasty, residual stenosis was graded as mild, moderate, and severe between 0-25%, 25-50%, and 50-75%, respectively. We recorded complications of the angiographic procedures, such as arterial dissection, vascular perforation, and acute occlusion (thrombosis).

Procedure

After local anesthesia with 20 mg/mL lidocaine, a 7.0- to 8.0-F guide sheath was inserted via the ipsilateral or contralateral common femoral artery. Unfractionated heparin (5000 IU) was injected via the sheath. Drug-eluting balloon angioplasty (Extender; Invamed, Ankara, Türkiye) was performed in all patients, and calcification density was reduced by atherectomy (Temren atherectomy device; Invamed, Ankara, Türkiye) before angioplasty. The entire lesions were routinely dilated with long balloons of 2- to 7-mm in diameter. If flow-restricting dissection occurred after dilation with long balloons, additional balloon dilation was performed at the surgeon's discretion.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Mean, median, first quartile, and third quartile were used to express continuous variables, whereas numbers and percentages were used to express categorical variables. Missing data were excluded from statistical analysis. Differences between the two groups were analyzed using the t-test. Categorical variables were compared using the chi-square test and the exact test. The Wilcoxon test was applied for dependent variables that were

Characteristics	Demographic and clinical characteristics of the patients											p	
	Total (n=192)			≤1 min (n=105)				>2 min (n=87)					
	n	%	Mean±SD	Range	n	%	Mean±SD	Range	n	%	Mean±SD		Range
Age (year)			66.1±9.7	42-94			66.6±9.7	46-94			65.6±9.8	42-83	0.499 t=0.678
Sex													0.040
Male	158	82.3			81	77.1			77	88.5			
Female	34	17.7			24	22.9			10	11.5			
Body mass index (kg/m ²)													<0.001
18.5-24.9	123	64			88	83.8			35	40.2			
25-29.9	52	27.1			14	13.3			38	43.7			
30-34.9	14	7.3			2	1.9			12	13.8			
35-39.9	1	0.5			0.0	0.0			1.0	1.1			
≥40	2	1.0			1	1.0			1.0	1.1			
Hypertension	103	53.6			58	55.2			45	51.7			0.627
Diabetes mellitus	84	43.8			45	42.9			39	44.8			0.784
Hyperlipidemia	77	40.1			47	44.8			30	34.5			0.148
Chronic renal disease	18	9.4			7	6.7			11	12.6			0.157
Coronary artery disease	75	39.1			40	38.1			35	40.2			0.763
Smoker	139	72.4			73	69.5			66	75.9			0.128

SD: Standard deviation.

nonnormally distributed. A p-value <0.05 was considered statistically significant.

RESULTS

The mean age was 66 ± 9.7 (range, 42-94) years, which meant no statistical difference between the groups ($p=0.499$; Table 1). One hundred fifty-eight (82.3%) patients were male; 88.5% had prolonged balloon inflation times, and 77.1% had shortened balloon inflation times ($p=0.040$). Patients' body mass indices (BMIs) were examined; 121 (63%) patients had normal BMI. When comparing BMIs between the groups, 88 (83.8%) patients with shortened balloon inflation times had normal BMIs; in contrast, 35 (40.2%) patients with prolonged balloon inflation times had normal BMIs ($p<0.001$). A total of 103 (53.6%) patients had hypertension, 84 (43.8%) had diabetes, 77 (40.1%) had hyperlipidemia, 18 (9.4%) had chronic renal failure, and 75 (39.1%) patients had coronary artery disease. The distribution of comorbidities did not differ between the groups (all $p>0.005$; Table 1). One hundred thirty-nine (72.4%) patients were smokers. Medication history was evaluated, and 141 (59%) patients had used antiplatelet therapy (acetylsalicylic acid, clopidogrel, or a combination), 29 (12.1%) patients had used anticoagulant therapy (warfarin sodium or direct oral anticoagulants), and 37 (15.5%) had used cilostazol therapy.

The superficial femoral artery was the most commonly processed artery, with 167 (69.9%) patients (Table 2). The median lesion length was 80 (interquartile range [IQR], 70-90) mm. The median balloon diameter was 6 (IQR, 4-6) mm, and the median balloon length was 120 (IQR, 100-120) mm. The median inflation pressure was 9 (IQR, 8-10) atmospheres. There was no statistical difference between the prolonged and shortened balloon inflation time groups for median balloon diameters, lesion lengths, and inflation pressures ($p>0.05$; Table 2).

It was observed that the preoperative angiograms of most patients showed moderate and severe stenosis (Table 2). There was no statistical difference between the groups regarding balloon inflation time for preoperative stenosis ($p=0.738$). Postoperative residual stenosis was milder in the group with prolonged balloon inflation times than in the group with shortened balloon inflation

times, with predominantly moderate stenosis ($p<0.001$). Severe residual stenosis was observed postoperatively in eight patients with shortened balloon inflation times. The Wilcoxon test was applied to assess the preoperative and postoperative stenosis levels in patients, and results revealed a statistically significant difference ($p<0.001$). All of these patients had a history of smoking; no severe residual stenosis was observed in nonsmokers ($p=0.109$).

Complications that occurred after angioplasty were dissection in 16 patients, thrombosis in two patients, and perforation in one patient. Five of these patients were in the group with prolonged balloon inflation times. The result was insignificant when comparing complications according to two different balloon inflation times, but insufficient numbers may have affected this ($p=0.257$). One patient who developed thrombosis was treated with mechanical aspiration, and another patient with perforation was treated with a covered stent, resulting in no morbidity or mortality.

DISCUSSION

Endovascular techniques, including drug-eluting balloons and bailout stenting, have become effective alternatives for treating infrainguinal PAD.^[12] Among the critical factors in angioplasty, balloon inflation time is potentially significant yet underinvestigated. The use of standard balloons (semicompliant/noncompliant) in preparing lesions and using prolonged inflations (>180 sec) increased procedural success rates and long-term patency. Furthermore, it reduces the risk of arterial dissection.^[13] In another study, harvested porcine carotid arteries were used in an *ex vivo* pulsatile flow bioreactor system. Using drug-coated balloons, balloon inflation times and transit times were used to calculate the amount of drug passing into the vein. As a result, it was observed that the drug passing into the vein was better when the balloon inflation time was increased and the transit time was decreased.^[14]

Although several studies have examined the optimal duration of balloon inflation, the evidence remains inconclusive, and clinical practice continues to vary based on individual surgeon preference.^[7] Thus, this study aimed to evaluate the impact of short versus prolonged balloon inflation

Table 2
The characteristics of procedure and lesion

Characteristics	Total (n=239)			Balloon inflation time (min)						p				
	n	%	Median	IQR	<1 min (n=138)			>2 min (n=101)						
					n	%	Median	IQR	n		%	Median	IQR	
Balloon diameter (mm)			60	40-60										
Balloon length (mm)			120	100-120										
Inflation pressure (atm)			9	8-10										
Lesion length (mm)			80	70-90										
Location of the lesion														
Superficial femoral artery	167	69.9			101	73.2			66	65.3				0.785
Popliteal artery	22	9.2			13	9.4			9	8.9				<0.001
Infrapopliteal artery	50	20.9			24	17.4			26	25.7				0.476
Preoperative stenosis														0.294
50	37	15.5			23	16.7			14	13.9				0.290
50-75	105	43.9			58	42			47	46.5				
75-100	97	40.6			57	41.3			40	39.6				
Postoperative residual stenosis														<0.001
0-25	147	61.5			59	42.8			88	87.1				
25-50	84	35.1			71	51.4			13	12.8				
50-75	8	3.3			8	5.8			-	-				
Complications														0.257
Dissection	16	6.6			11	8			5	5				
Thrombosis	2	0.8			2	1.4			-	-				
Perforation	1	0.4			1	0.7			-	-				

IQR: Interquartile range.

times on angiographic outcomes, using standardized procedural techniques across all patients.

Historically, when balloon angioplasty was first introduced, early randomized trials supported the immediate benefits of prolonged inflation, though these advantages were not always maintained over time.^[15-17] In early methods, a 1-min inflation duration was common, yet often used without a clearly defined rationale.^[18] More recent work by Zorger et al.^[17] demonstrated improved early angiographic results and reduced dissection rates with balloon inflation times exceeding 3 min in femoropopliteal lesions. Similarly, Elens et al.^[18] reported that inflation times of 3 to 5 min produced superior angiographic outcomes and minimized the need for additional interventions.^[15]

Our study aligns with these findings, demonstrating that prolonged inflation (>2 min) significantly reduces residual stenosis and arterial dissection compared to inflation durations ≤1 min. Importantly, these benefits were observed without increased procedure-related complications such as thrombosis or perforation.

However, concerns have been raised about the potential risks of extended balloon inflation. In animal studies, durations longer than 60 sec were associated with endothelial injury, inflammation, and subsequent intimal hyperplasia, raising questions about long-term vascular healing.^[19-21] Although our findings suggest promising immediate angiographic outcomes, the long-term impact of prolonged balloon inflation on restenosis and vessel integrity remains uncertain.

Prolonged balloon inflation has several advantages: it is easily implemented in routine practice, requires no additional devices, and may reduce the need for bailout stenting. Additionally, adequate dilation and prolonged contact time may facilitate better drug delivery in drug-eluting balloons, enhancing the antiproliferative effect of agents such as paclitaxel.^[22-24]

Our study also supports the hypothesis that prolonged inflation may reduce the risk of severe dissection, as suggested by Fujihara et al.,^[25] who found that longer inflation times significantly lowered dissection rates in similar lesion types.^[21] However, it is also possible that extended inflation may temporarily mask dissections, which could later

result in acute occlusion if not adequately addressed intraoperatively. Therefore, careful post-dilation imaging and clinical monitoring remain essential.

Moreover, while our findings demonstrate significant short-term advantages of prolonged inflation, persistent risk factors, such as smoking, diabetes, and hyperlipidemia, may continue to influence mid- and long-term outcomes. Interestingly, all cases of severe residual stenosis in our cohort occurred in smokers, although the association was not statistically significant.

This study had several limitations. First, its retrospective design inherently limited the ability to establish causality. Second, the relatively small sample size may have restricted the generalizability of the findings and reduced the power to detect specific differences between groups. Additionally, balloon inflation time was not strictly standardized and may have varied based on individual surgeon discretion, introducing a potential source of bias. Although all procedures were performed at a single center using standardized protocols, not all interventions were conducted by the same operator, which may have influenced angioplasty outcomes. Furthermore, not all procedures recorded actual inflation pressure and balloon deflation velocity, limiting further procedural comparisons. Lastly, this study focused solely on immediate postprocedural outcomes; long-term follow-up data were unavailable, including restenosis rates and target lesion revascularization.

In conclusion, while many studies attribute improved patency to using drug-eluting balloons, it is worth reconsidering the role of balloon inflation time as a potentially critical factor in optimizing outcomes. The improved patency associated with drug-eluting balloons may partly depend on sufficient drug transfer, which, in turn, is influenced by the duration of balloon contact with the vessel wall. This study demonstrated that balloon inflation times exceeding 2 min reduce residual stenosis and complications such as dissection. Nonetheless, well-designed, prospective randomized controlled trials are needed to validate these findings and determine the optimal balloon inflation duration for different lesion types and patient subgroups.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Impact of longitudinal versus oblique groin incisions on femoral wound healing in endovascular aortic repair patients

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ABSTRACT

Objectives: This study aimed to examine the wound healing problem development status of the longitudinal and oblique incision types applied in our clinic.

Patients and methods: A total of 201 patients (183 males, 18 females; 66.9±9.9 years; range, 34 to 88 years) who underwent emergency or elective abdominal aortic aneurysm endovascular aortic repair (EVAR) or thoracic endovascular aortic repair (TEVAR) between September 2014 and June 2021 were included in this single-center retrospective study. Group 1 (n=115) consisted of patients who underwent longitudinal (vertical) femoral incision, whereas Group 2 (n=86) underwent oblique (transverse) femoral incision. Preoperative risk factors connected with wound healing problems, femoral wound healing problem development, onset time of the femoral wound healing issues, types of the wound healing issue, hospital stay, and mortality were assessed.

Results: Femoral wound healing problems were significantly lower in Group 2 (p<0.05). It was observed that wound healing problems started earlier in Group 1. The distribution of diabetes mellitus, chronic kidney disease, and peripheral artery disease rates did not differ significantly (p>0.05). Obesity and chronic obstructive pulmonary disease rates were significantly higher in Group 1 (p<0.05). Postoperative length of hospitalization were borderline statistically significant in Group 1 (p=0.076). The incidence of early mortality was similar.

Conclusion: Femoral wound healing problems were observed more frequently in patients who underwent EVAR with femoral longitudinal incision access. Fewer wound healing problems in the oblique incision group made us routinely prefer the oblique incision in femoral artery access in EVAR cases.

Keywords: EVAR, incision, groin, longitudinal, oblique, TEVAR, transverse, vertical, wound healing, wound infection.

In 1991, before Parodi et al.,^[1] open surgery was defined as the only interventional treatment option for thoracic and abdominal aortic aneurysms and dissections. Nowadays, endovascular aortic treatment methods have become increasingly widespread and have emerged as a standard treatment modality for thoracic and abdominal aortic aneurysms, dissections, and ruptures.^[2,3] In the endovascular aortic repair (EVAR) procedure, the femoral artery is used as the vascular access route. The groin region, which is the anatomical access point of the main femoral artery, is a moist, folding region and is especially ideal for microbial growth. Because of this nature of the inguinal region, there is a risk of wound infection and closure problems after open surgical access to the femoral artery. The most commonly used incision for the exposure of femoral

region is the longitudinal (vertical) incision.^[4] With a longitudinal incision, an incision is made from top to bottom perpendicular to the inguinal region to provide a good view of the vessels. Although this incision provides good surgical visualization, wound healing problems are more frequent and the risk of infection is higher.^[5] On the other hand, oblique (transverse) incision in the groin is associated with less impairment in lymphatic circulation and less

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wound healing complications. However, in addition to these advantages, surgical visualization of the femoral artery is more difficult.^[6] In our study, we aimed to evaluate the relationship between these different types of femoral incisions and wound healing problems with our own data.

PATIENTS AND METHODS

This single-center retrospective study included a total of 201 patients (183 males, 18 females; 66.9 ± 9.9 years; range, 34 to 88 years) who underwent emergency and elective EVAR and thoracic endovascular aortic repair (TEVAR) procedures in the Cardiovascular Surgery Department of the Sakarya University Training and Research Hospital from September 2014 to June 2021. Patients were divided into two groups: Group 1 and 2 depending on the femoral incision type. Group 1 is consist of longitudinal femoral incision group and Group 2 is oblique femoral incision group. Group 1 (n=115) consisted of patients who underwent longitudinal (vertical) femoral incision, whereas Group 2 (n=86) underwent oblique (transverse) femoral incision. A longitudinal incision was preferred in the EVAR procedures performed until the mid-2018s from the beginning as the standard incision type to access the femoral artery. Due to femoral wound healing issues, our standard incision type was changed to an oblique groin incision in mid-2018s after an analysis of the data in the literature. Since then, we have exclusively used the oblique groin incision for EVAR procedures. Written informed consent was obtained from all participants. The study protocol was approved by the Sakarya University Ethics Committee (Date: 23.11.2018, No: 71522473/050.01.04/281). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Surgical procedure

Endovascular procedures were performed in the angiography unit with the same surgical team. Anaconda Abdominal Aortic Stent Graft System (Vascutek, Terumo, Inchinnan, Scotland), Medtronic Endurant II Stent Graft System (Medtronic Vascular, Santa Rosa, CA, USA), Medtronic Valiant Thoracic Stent Graft System (Medtronic Vascular, Santa Rosa, CA, USA), and Ankura Abdominal Aortic Stent Graft System (Lifetech Scientific, Shenzhen, China) were used as

endovascular stent grafts for the procedures. All operations were performed under general anesthesia. Femoral arteries were used for vascular access. Depth and the length of the incisions were similar. Femoral arteries were not excessively explored to avoid further complications. A simple 5-0 Prolene purse-string suture was placed on the anterior side of the femoral artery to control the arterial bleeding during the procedure. The subcutaneous tissue was closed with 1-0 polyglactin (Vicryl) suture. The skin was closed with 3-0 Prolene sutures with a vertical mattress suture technique in all patients. Postoperative routine follow-up was done on the 10th day, at three month and six months, at one year, and annually thereafter following discharge.

Data were collected from the patient files and hospital's online database. Demographic values, preoperative risk factors connected with abdominal aortic aneurysms and wound healing issues, femoral wound healing issues, onset of the femoral wound healing issue, urgent and elective status, types of the wound healing problem, wound culture tests, intensive care unit and hospital stay, and mortality were assessed. Postoperative early mortality was defined as deaths within 30 days after the operation.

Wound healing problems were determined as follows: wound dehiscence, superficial surgical site infection, deep surgical site infection, and lymphatic leak. There were no cases of organ/space surgical site infection; therefore, this category was excluded from the tables.

Statistical analysis

Data were analyzed using IBM SPSS version 27.0 software (IBM Corp., Armonk, NY, USA). Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov test. The independent sample t-test was used to analyze quantitative independent data with normal distribution. The Mann-Whitney U test was used to analyze quantitative independent data with nonnormal distribution. The chi-square test was used in the analysis of qualitative independent data, and the Fischer test was used when chi-square test conditions were not met. A p-value <0.05 was considered statistically significant.

RESULTS

Age and sex distribution of the patients did not differ significantly between Groups 1 and 2 ($p>0.05$). The distribution of hypertension (HT), diabetes mellitus (DM), chronic kidney disease (CKD) and peripheral artery disease (PAD) rates did not differ significantly between the two groups ($p>0.05$). Obesity was significantly ($p=0.020$) lower in Group 2 (1.2% $n=1$) than in Group 1 (8.7% $n=10$). Chronic obstructive pulmonary disease (COPD) were significantly ($p=0.014$) lower in the Group 2 (29.1% $n=25$) than in the longitudinal incision group (46.1% $n=53$). Smoking rates did not differ significantly between the groups ($p=0.821$; Table 1).

There was no significant difference between Groups 1 and 2 in terms of the rate of aneurysm, dissection, and rupture diagnoses at the time of intervention ($p>0.05$; Table 1). Urgent and elective intervention status of the patients resulted similarly and no statistical difference was found (Table 1).

The number of patients with femoral wound healing problems was compared for statistical analysis. Three patients had both wound dehiscence

and lymphatic leak in one groin in Group 1. As the statistical analysis was based on the number of patients rather than the number of complications, these cases were each counted as a single femoral wound healing problem to avoid duplication (Table 2). Femoral wound healing problems were significantly ($p=0.042$) lower in Group 2 (7.0% $n=6$) than in Group 1 (16.5% $n=19$). Although the onset of postoperative femoral wound healing problems did not differ significantly ($p=0.13$) between Group 1 (12.8 ± 8.9 days) and Group 2 (19.0 ± 6.3 days), it was observed that wound closure problems started earlier in Group 1. There was no significant difference between the both groups in terms of wound culture results and rates of different wound closure problems ($p>0.05$; Table 2).

There was no significant difference in the reoperation rate and in terms of intensive care unit length of stay between the both groups ($p>0.05$). Postoperative length of hospitalization between the both groups were borderline statistically significant ($p=0.076$). Postoperative early mortality was similar between the groups (Table 2).

Treatment methods used in the wound healing process are summarized in Table 3.

Table 1
Demographic and preoperative data comparison of both groups

	Longitudinal incision				Oblique incision				<i>p</i>
	n	%	Mean±SD	Median	n	%	Mean±SD	Median	
Age (year)			67.0±9.9	68.0			66.8±10.0	70.0	0.711*
Sex									0.100†
Female	7	6.1			11	12.8			
Male	108	93.9			75	87.2			
Hypertension	104	90.4			76	88.4			0.636†
Diabetes mellitus	17	14.8			12	14.0			0.869†
Obesity	10	8.7			1	1.2			0.020†
Chronic kidney disease	22	19.1			11	12.8			0.230†
Peripheral artery disease	44	38.3			22	25.6			0.058†
COPD	53	46.1			25	29.1			0.014†
Cigarette smoking	61	53.0			47	54.7			0.821†
Aneurysm (+)	114	99.1			85	98.8			1.000†
Dissection (+)	24	20.9			14	16.3			0.411†
Rupture (+)	24	20.9			11	12.8			0.135†
Emergent (+)	30	26.1			15	17.4			0.146†
Elective (+)	85	73.9			71	82.6			0.146†

SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; * Mann-Whitney U test; † Chi-square test (Fischer test).

Table 2
Postoperative data between groups

	Longitudinal incision				Oblique incision				p
	n	%	Mean±SD	Median	n	%	Mean±SD	Median	
Femoral wound healing problem¶	19	16.5			6	7.0			0.042 †
Onset of femoral wound healing problem (d)			12.8±8.9	12.0			19.0±6.3	20.5	0.130†
Wound culture									1.000†
(-)	16	84.2			5	83.3			
(+)	3	15.8			1	16.7			
Wound dehiscence	16	13.9			4	4.7			0.562†
SSI-superficial	3	2.6			1	1.2			1.000†
SSI-deep	0	0.0			1	1.2			0.240†
Lymphatic leak*	3	2.6			0	0.0			0.133‡
Reoperation	13	11.3			8	9.3			0.646†
ICU stay (day)			2.9±6.1	1.0			2.3±2.6	1.0	0.508*
Hospital stay (day)			8.3±8.1	6.0			6.8±5.3	5.0	0.076 *
Operative mortality	0	0			0	0			
Postoperative early mortality									0.189†
(-)	110	95.7			85	98.8			
(+)	5	4.3			1	1.2			

SD: Standard deviation; SSI: Surgical site infection; ICU: Intensive care unit; ¶ Described in the article above; * Mann-whitney u test; † Chi-square test (Fischer test); ‡ Independent sample t-test.

Table 3
Treatment methods used in the wound healing process in patients who had wound closure problems depending on the incision type

	Number of patients with incision type and wound closure problems	
	Longitudinal (n=19)	Oblique (n=6)
	n	n
Debridement + surgical closure	4	4
Vacuum assisted closure + surgical closure	10	
Secondary healing with local dressing	5	2

DISCUSSION

Surgical site infections are one of the most common complications after vascular surgery and an important cause of morbidity that may progress to prolonged hospitalization, graft-related complications, and even limb loss.^[7] Apart from increased morbidity, another important situation is that the wound healing issues cause prolonged hospitalization with repeated interventions applied

during the wound closure process, which leads to increased health care costs.^[8] The incidence rate of surgical wound complications, such as infection, hematoma, and lymphatic drainage ranges from 1 to 10%^[9] to 4.8%,^[10] and a meta-analysis by Ng et al.^[6] showed that close to 30% of patients were affected by surgical wound infection after surgery in the femoral region despite all preoperative, intraoperative, and postoperative precautions. In our study, 25 (12.4%) of a total of 201 patients developed

femoral surgical wound healing problems, and only five (2.48%) of these patients developed surgical site infection, with similar results to the literature.

According to the classification of the Centers for Disease Control and Prevention (CDC), surgical wound infections are divided into three classes.^[11] These were classified as superficial incisional, deep incisional, and organ/space surgical site infections, and this classification was standardized accordingly. In these specific incision types we compared in the femoral region, organ/space surgical site infection was not compared in our study because there was no such deep organ/space level in this region. However, since superficial incisional surgical site infections are classified with a wide range of regions including epidermal, dermal, and subcutaneous tissue, we evaluated patients with wounds that did not reach the subcutaneous tissue and had only a mechanical closure problem in the skin in a separate class as “wound dehiscence.”

The rate of wound healing problems in the longitudinal incision group was statistically significantly higher than in the oblique incision group ($p=0.042$). In the literature, prospective, randomized controlled, and meta-analysis studies also show that infection and wound healing problems are more common in longitudinal incisions compared to oblique incisions.^[4-6] In all patients in whom wound dehiscence was observed, this was encountered as a partial closure problem. When compared according to the CDC’s surgical site infection classification, there was no statistically significant difference between the groups. In addition to the patients with wound dehiscence, three patients with accompanying lymphatic leakage were in the longitudinal incision group and were evaluated under this group. No lymphatic complications were observed in the oblique incision group.

Although there was no statistically significant difference in the timing of the onset of wound healing problems, it was observed that these problems started earlier in the longitudinal incision group. Although the onset time is not discussed in many articles in the literature, in the randomized controlled study of Swinnen et al.,^[5] it was mentioned that the infection developed by the 10th day in a significant portion of the patients with wound infection and the infection developed by the 28th day in a large portion of the remaining patients. In our study, wound healing

problems were observed on average on the 12th day in the longitudinal incision group and on the 20th day in the oblique incision group. This suggests that oblique incisions have a lower incidence of healing issues with a later onset of healing complications.

When the duration of hospitalization was analyzed, it was observed that hospitalization in the longitudinal incision group was borderline statistically significant ($p=0.076$). This result may be attributed to the earlier onset of wound healing problems in the longitudinal incision group and longer hospitalization for this reason. Siracuse et al.^[12] also showed that the longitudinal incision access group was hospitalized statistically longer than the oblique incision access group in their study in which they compared the results according to access route differences. Prolonged hospitalization increases both economic costs and the burden of healthcare services. Therefore, fewer wound healing problems will positively contribute to this additional cost-effectiveness analysis and patient bed occupancy rate.

No statistically significant difference was found between the two groups in terms of operative and postoperative mortality. Similarly, no statistically significant difference was observed in the literature according to incision type.^[12,13] Similarly, there was no significant difference between the reoperation rates except for surgical wound healing problems.

Advanced age, female sex, DM, obesity, cigarette smoking, dialysis-dependent CKD, PAD, COPD are considered factors that increase the risk of developing surgical site infection in previous studies.^[7,14,15] When we analyzed our preoperative demographic data, there was no significant difference in terms of patient age and sex. Diabetes mellitus in itself is a risk factor in the development of atherosclerosis and leads to adverse effects on wound healing with inadequate angiogenesis, impaired cellular response, and increased oxidative stress.^[16] In terms of DM, the data were similar between the two groups, and there was no statistically significant difference. Obesity is another factor that increases the risk of surgical wound infection not only in EVAR procedures but also in all other surgeries.^[17] Although the mechanism has not been fully explained, impaired microcirculation and immune system response, increased lymphedema, and negative effects on respiratory functions appear to be obesity-related

factors in impaired wound healing.^[18] It should again be emphasized that DM and atherosclerosis are more common in obese patients, and these have negative effects on the wound healing process. In our study, the rate of obesity in the longitudinal incision group, in which wound healing problems were observed more frequently, was statistically more significant than the other group ($p=0.020$). Peripheral artery disease, which adversely affects micro- and macrocirculation of the extremity and thus causes diminished tissue oxygenation, was borderline statistically significant in the longitudinal incision group ($p=0.058$), where wound healing problems were more common. Finally, the incidence of COPD, which is also associated with an increased risk of wound infection, was statistically significantly higher in the same group ($p=0.014$). In this context, tissue hypoxia caused by impaired respiratory functions in patient groups with COPD is interpreted as the main relationship.^[17]

Treatment modalities used in the wound healing process were classical wound debridement and healing with simple suturization, healing with vacuum-assisted closure devices, and, finally, suturization of the wound. In some patients, secondary healing with local dressing applications was applied. Skin grafting or skin flap application methods were not required in any patient who developed wound healing problems.

Wound healing is an important postoperative complication and requires attention as it requires additional surgical intervention, prolongs hospitalization, and may sometimes lead to limb loss and mortality. In previous studies, EVAR was compared to open surgery were shown to be effective and safe in the early period,^[19] which increased the preference for endovascular procedures in appropriate patients. However, in the current era of advanced surgical techniques, new approaches are being explored to minimize possible wound healing complications. Nowadays, percutaneous methods have also started to be used in femoral access, and studies in the literature comparing open surgical and percutaneous access in the femoral access route^[20] will contribute to the practice in terms of surgical interventions with less femoral wound closure issues, at least for endovascular procedures in the future.

This study had some limitations. Although most of the risk factors were similar in the preoperative

group comparison, the fact that risk factors such as obesity, COPD, and to a lesser extent PAD (borderline statistically significant in this study), which may have a negative effect on femoral wound healing, were higher in the longitudinal incision group, raises additional questions as to whether adverse wound healing occurred only due to the type of incision or also with the effect of these risk factors. The retrospective design is another limiting factor, and comparing different incisions with prospective randomized controlled studies would provide more robust results. The number of patients is relatively sufficient; nonetheless, a larger number would provide more statistically significant results.

In conclusion, femoral wound healing problems were observed more frequently in patients who underwent EVAR with longitudinal incision access from the femoral region in our study. Furthermore, wound healing problems started earlier, and hospitalization was longer in the longitudinal incision group. This prolongs treatment, leads to additional interventions, and ultimately increases treatment costs and patient bed occupation time. Therefore, surgical procedures that cause less femoral wound healing problems should be selected. The fact that the oblique incision group had fewer wound healing problems resulted in us routinely preferring the oblique incision for femoral access in EVAR.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, control/supervision, analysis, processing, literature review, writing the article, critical review, materials: H.S.; Idea/concept, data collection, analysis, idea/concept, data collection, analysis: H.İ.E; Materials, interpretation: B.P.; Materials, data collection, literature review: B.Ö.; Idea/concept, interpretation, critical review: İ.K.

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Long-term outcomes of Ross procedure in pediatric patients: A single-center experience

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ABSTRACT

Objectives: This study aimed to share a single-center experience with the Ross procedure in pediatric patients and to demonstrate that the need for reoperations due to autograft failure can be minimized with appropriate surgical technique.

Patients and methods: This single-center retrospective study analyzed 18 pediatric patients (16 males, 2 females; median age: 3 years; range, 4 months to 8 years) who underwent the Ross operation between January 2002 and January 2024. Surgical techniques, patient demographics, and outcomes were assessed. Statistical analysis was conducted using the Kaplan-Meier method for overall survival and freedom from reoperation.

Results: Early mortality was 5.5%, primarily due to sepsis and multiple organ failure. The 10-year survival rate was 94%, demonstrating favorable long-term outcomes. Two (11.1%) patients required reoperation for conduit dysfunction, with a 15-year freedom from conduit reintervention rate of 77%.

Conclusion: The Ross procedure in pediatric patients showed low mortality and morbidity rates, with excellent long-term survival outcomes. Effective surgical techniques and modifications were crucial in preventing autograft dysfunction and reducing reoperation rates. The study challenges the notion that the Ross procedure leads to the development of two valve diseases, emphasizing its significance as a preferred option for aortic valve replacement in children.

Keywords: Aortic valve disease, autograft growth, conduit dysfunction, pediatric cardiology, Ross procedure.

Children with severe aortic valve disease often require surgical intervention to restore valve function and prevent complications. Available surgical options include aortic valve repair, mechanical or biological valve replacement, and the Ross procedure. The Ross procedure involves replacing the diseased aortic valve with the patient's own pulmonary valve, while a valved conduit is used to reconstruct the right ventricular outflow tract (RVOT).^[1] This technique has gained popularity in pediatric and adolescent patients due to its superior hemodynamic profile, elimination of the need for long-term anticoagulation, and the ability of the autograft to grow with the patient, potentially reducing the need for future reoperations.^[2]

Another emerging alternative in pediatric aortic valve surgery is the Ozaki procedure, which involves the reconstruction of the aortic valve using autologous pericardium tailored to create new leaflets. The

Ozaki technique offers advantages, such as avoiding prosthetic material and preserving native aortic root geometry. However, its long-term durability in children remains under investigation, and it may not provide the same growth potential as the Ross procedure.^[3]

Despite these advantages, concerns persist regarding the potential for autograft insufficiency and degeneration of the conduit used for RVOT reconstruction over time, particularly in younger patients. This has led to the perception that the

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Ross procedure may “convert one valve disease into two valve diseases.”^[4]

Nevertheless, it is important to contextualize this view. While conduit reintervention may be required, the overall outcomes of the Ross procedure, including freedom from autograft dysfunction and excellent long-term survival, have challenged this perception.^[5] This study aimed to share our single-center experience with the Ross procedure in pediatric patients and to demonstrate that with appropriate surgical technique, the need for reoperations due to autograft failure can be minimized.

PATIENTS AND METHODS

This retrospective study included 18 pediatric patients (16 males, 2 females; median age: 3 years; range, 4 months to 8 years) who underwent the Ross operation at the Ege University Faculty of Medicine Department of Pediatric Cardiovascular Surgery between January 2002 and January 2024. Data were obtained from hospital records, national medical databases, and telephone interviews with patients followed up at external centers. Inclusion criteria were as follows: (i) diagnosis of severe aortic valve disease requiring surgical replacement, (ii) age below 18 years at the time of surgery, and (iii) complete availability of operative and follow-up data. Patients with incomplete records or follow-up shorter than 12 months were excluded. Written informed consent was obtained from the parents and/or legal guardians of the patients. The study protocol was approved by the Ege University Faculty of Medicine Ethics Committee (Date: 25.01.2024, No: 2024-2174 24-1.1T/53). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Follow-up included scheduled outpatient visits and regular transthoracic echocardiography evaluations. For patients not followed at our institution, follow-up status and echocardiographic data were obtained via structured telephone interviews with patients or their guardians. Early mortality was defined as death occurring within 30 days of the operation or before hospital discharge.

Surgical technique

All patients were operated on under cardiopulmonary bypass (CPB) with aortobicaval

cannulation via median sternotomy. Myocardial arrest was achieved with blood cardioplegia administered through the aorta or directly into the coronary ostia following aortotomy, depending on the presence of aortic insufficiency.

Aortotomy was performed 1 cm above the coronary ostia. The coronary artery buttons were excised and preserved. Aortic valve leaflets were resected. The pulmonary autograft was harvested after transecting the pulmonary artery at the bifurcation level. With a Hegar dilator placed through the right ventricle, an incision was made 5 to 10 mm below the pulmonary valve in the infundibulum. Care was taken to avoid injury to the first septal artery during autograft harvesting.

In cases of significant mismatch between the aortic annulus and pulmonary autograft, plication of the noncoronary and left coronary trigones was performed using pledgeted pericardial sutures. In patients with severely hypoplastic aortic annulus, the Ross procedure was combined with a Konno enlargement.

The pulmonary autograft was implanted into the native aortic position using interrupted 4/0 nonabsorbable multifilament sutures (Figure 1). The coronary buttons were reimplanted into the neo-aortic root using running prolene sutures. The distal aortic anastomosis was then completed using running sutures.

The RVOT was reconstructed using either pulmonary homografts, aortic homografts, bovine jugular vein conduits (Contegra; Medtronic, MN, USA), or porcine pericardial conduits (BioConduit®; BioIntegral Surgical Inc., Mississauga, Canada). The distal anastomosis was carefully fashioned to prevent stenosis. The conduit size was selected to match patient anatomy, with a moderately large size (conduit Z-score from 0 to +2).

All patients were evaluated intraoperatively with transesophageal echocardiography after weaning from CPB. Postoperative patients were evaluated with transthoracic echocardiography both before and after discharge and at regular intervals.

Statistical analysis

Jamovi version 2.5.2 was used for all statistical analyses. Categorical variables were presented as frequencies and percentages. Continuous variables were expressed as median (range). Survival and

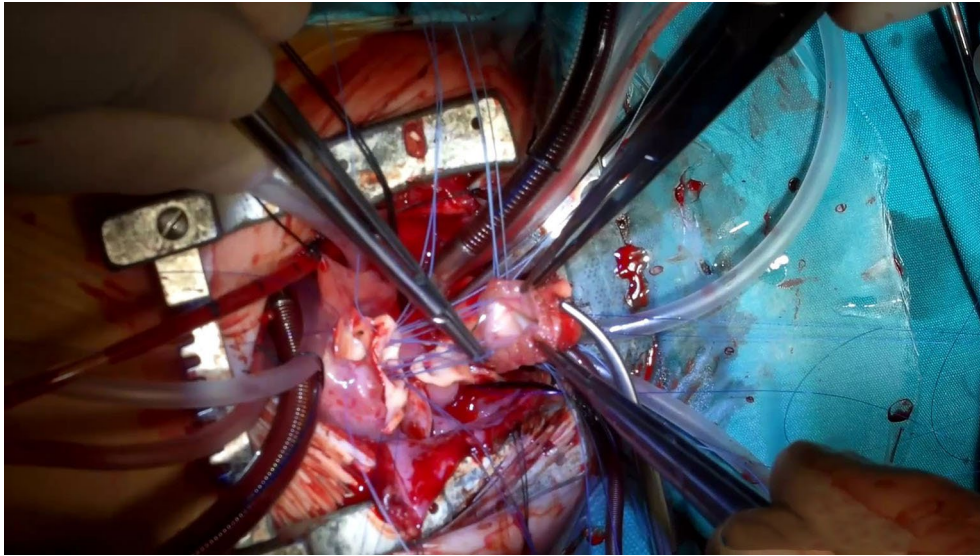


Figure 1. An intraoperative image of the youngest patient, a four-month-old male patient, showing implantation of a pulmonary autograft into the aortic annulus with separated sutures. The yellow circle indicates the pulmonary autograft, the blue oval shape indicates the aortic annulus, the blue star indicates the excised button-shaped left coronary, and the yellow star indicates the right coronary ostium.

freedom from reoperation were estimated using the Kaplan-Meier method. Reintervention was defined as any surgical procedure involving the RVOT conduit or autograft. A p value <0.05 was considered statistically significant.

RESULTS

The median weight was 13 kg (range, 4.6 to 25 kg). Four (22%) patients were infants. Eight (44%) patients had a bicuspid aortic valve, and one patient had Shone complex. Eleven patients had isolated aortic stenosis, three had isolated regurgitation, and four had mixed lesions.

Twelve (66.6%) patients had a history of balloon valvuloplasty, and one had prior surgical commissurotomy. Two (11.1%) patients required preoperative mechanical ventilation and inotropic support, both undergoing urgent surgery.

Two patients had left ventricular outflow tract obstruction. One of these patients underwent the Ross-Konno procedure, and the other underwent subaortic discrete membrane resection. In a case with annulus-pulmonary autograft mismatch, trigonal plication was performed. No reinforcement technique was used for autograft support.

For RVOT reconstruction, pulmonary homografts were used in 14 patients, aortic homografts in two, Contegra conduit in one, and porcine pericardial conduit in one patient. Conduit sizes ranged from 14 to 22 mm. The distal anastomosis was fashioned to avoid stenosis. Three patients underwent concomitant atrial septal defect closure, and one had subaortic discrete membrane resection. Mean cross-clamp and CPB times were 153 ± 18 and 171 ± 17 min, respectively. No intraoperative mortality occurred. Demographic and operative data of the patients are summarized in Table 1.

Two patients required prolonged ventilation (>24 h), both of whom had preoperative mechanical ventilation. One patient underwent delayed sternal closure at 36 h postoperatively. Early mortality occurred in one high-risk patient (two-year-old weighing <10 kg) who developed sepsis and multi-organ failure on postoperative Day 21. No late mortality was observed. The five-year survival rate was 94% (Figure 2).

The mean follow-up duration was 83.8 ± 65 months (range, 12 months to 10 years). Two (11.1%) patients underwent reoperations due to conduit dysfunction (one with pulmonary homograft at year seven and another with porcine pericardial conduit at year three). No autograft reintervention

Table 1
Demographic, echocardiographic, and operative data of patients (n=18)

Variables	n	%	Mean±SD	Median	Range
Age (year)				3	4 months - 8 years
Weight (kg)				13	4.6-25
Sex					
Male	16	88.9			
Female	2	11.1			
Bicuspid aortic valve	8	44.4			
Shone complex	1	5.5			
Dominant aortic valve lesion					
Stenosis	11	61.1			
Insufficiency	3	16.7			
Mixed lesion	4	22.2			
Previous balloon valvuloplasty	12	66.6			
Previous surgical commissurotomy	1	5.5			
Preoperative mechanical ventilation	2	11.1			
Urgent surgery	2	11.1			
Concomitant surgery	4	22.2			
Atrial septal defect closure	3	16.7			
Subaortic discrete membrane resection	1	5.6			
Ross-Konno procedure	1	5.6			
Aortic annulus trigone plication	1	5.6			
Cardiopulmonary bypass time (min)			171±17		
Cross-clamp time (min)			153±18		
Conduits used for RVOT reconstruction					
Pulmonary homograft	14	77.8			
Aortic homograft	2	11.1			
Contegra	1	5.6			
Porcine pericardial conduit	1	5.6			
Conduit sizes (mm)					14-22
Postoperative prolonged ventilation	2	11.1			
Delayed sternal closure	1	5.6			
Early mortality	1	5.6			
Late mortality	0	0			
Reoperation due to conduit failure	2	11.1			
Autograft dysfunction/reintervention	0	0			
Mean follow-up duration			83.8±65		12 months - 10 years

SD: Standard deviation; RVOT: Right ventricular outflow tract.

or dysfunction was observed. Five-year freedom from reoperation was 90% (Figure 3). Due to the small cohort with longer follow-up, 10- and 15-year Kaplan-Meier estimates were not statistically reliable and were therefore not reported.

All surviving patients showed appropriate growth of the pulmonary autograft in serial echocardiograms, with preserved Z-score values and no significant autograft insufficiency. None had aneurysmal dilation or stenosis.

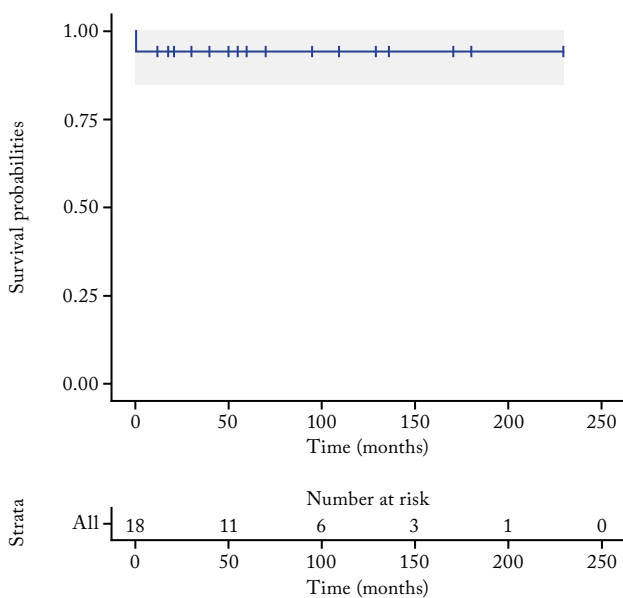


Figure 2. Kaplan-Meier plot showing patient survival.

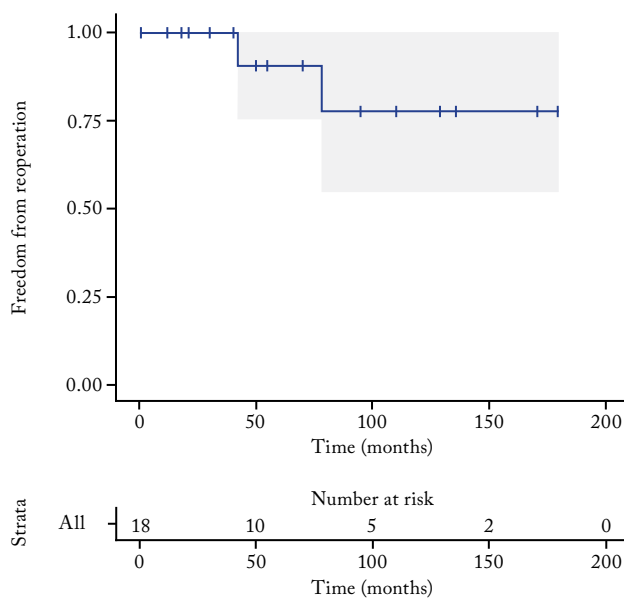


Figure 3. Kaplan-Meier plot showing freedom from reoperation.

DISCUSSION

The Ross procedure offers several advantages over traditional prosthetic valve replacements in pediatric patients, including optimal hemodynamics, avoidance of anticoagulation, and potential for somatic growth. These characteristics are particularly valuable in the growing child.^[5,6] Our study contributes to the evidence supporting the use of the Ross procedure in children by presenting a favorable early outcome, low reoperation rates, and preserved autograft function during mid-term follow-up.

Our observed early mortality rate (5.5%) is consistent with previous pediatric series, where rates have ranged from 0 to 16% depending on age and risk profile.^[7,8] The single mortality in our cohort occurred in a critically ill infant who underwent emergency surgery after prior balloon valvuloplasties and presented with organ dysfunction. These risk factors are well-documented predictors of poor outcome.^[4,9]

Importantly, there were no cases of late mortality. Five-year survival was 94%, which aligns with the outcomes reported in recent systematic reviews and registry studies in pediatric cohorts.^[10]

No autograft dysfunction or reoperation was observed in our series. This is a noteworthy finding,

as prior studies have reported autograft failure rates of approximately 1% per year.^[9] Several factors may account for our favorable results, including the use of precise surgical techniques such as interrupted sutures at the proximal anastomosis to preserve geometry, avoidance of reinforcement that may limit growth, and inclusion technique rather than full root replacement. However, the absence of autograft-related complications must be interpreted cautiously, as some patients were followed at external centers and limited follow-up beyond 10 years reduces long-term reliability. We acknowledge that the possibility of unreported dysfunction due to loss to follow-up remains.

To prevent conduit degeneration, homografts were preferentially used. Nevertheless, two patients required conduit replacement due to degeneration—one with a pulmonary homograft at year seven, and the other with a porcine pericardial conduit (BioIntegral Surgical Inc., Mississauga, Canada) at year three. The early failure of the latter is consistent with literature describing an inflammatory response and premature degeneration associated with this material.^[11] Our five-year freedom from reoperation was 90%, comparable to prior reports of 79 to 90%.^[12,13]

Aortic root dilatation or aneurysm formation did not occur in any of our patients during follow-up.

We attribute this to the use of subcoronary implantation and the natural anatomical integration of the pulmonary autograft. Reinforcement techniques, while sometimes effective in adults, are not routinely used in children due to concerns over growth limitation.^[9,14,15]

Regarding alternative techniques, the Ozaki procedure has emerged as a promising reconstructive option in pediatric aortic valve disease. It offers avoidance of prosthetic materials and preserves native aortic root dynamics. However, long-term durability in children remains uncertain, and it lacks the growth potential offered by the Ross procedure. Further comparative studies are needed to define its role.^[3,16,17]

Intraoperative care to preserve the first septal branch during autograft harvest is essential, as injury may compromise myocardial perfusion. We emphasize that meticulous dissection was performed in all cases to prevent such complications.

No patient in this series required extracorporeal membrane oxygenation support, including the single early mortality case. Given the late deterioration and progression to multi-organ failure, extracorporeal membrane oxygenation was not initiated due to the poor likelihood of recovery and ongoing septic complications.

This study had several limitations. It was limited by a small sample size and single-center retrospective design. The follow-up period varied significantly between patients, and longer-term outcomes beyond 10 years were available for only a few patients, limiting statistical validity for long-term survival and reoperation estimates. Additionally, the absence of a comparison group and potential loss to follow-up in some cases restricts the generalizability of the findings. Despite these limitations, our results support the use of the Ross procedure as a favorable option for pediatric aortic valve replacement when performed by experienced surgeons.

In conclusion, this study demonstrated that the Ross procedure can be performed in pediatric patients with low mortality and morbidity. With appropriate surgical technique, the autograft can function well and grow with the patient, minimizing the need for reoperation. Our findings suggest that conduit-related reinterventions are manageable and do not outweigh the significant benefits of using the patient's own tissue. While vigilance in long-term

follow-up remains essential, the perception that the Ross procedure converts one valve disease into two may be overly pessimistic in the context of properly selected and managed pediatric patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, references and fundings, materials: O.N.T.; Design, literature review: O.N.T., Y.A.; Control/supervision, critical review: Y.A., R.E.L.; Data collection and/or processing, analysis and/or interpretation, writing the article: M.A., O.N.T.

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Successful endovascular treatment of carotid artery injury following hemodialysis catheter insertion

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ABSTRACT

Although arteriovenous fistulas are the first choice for hemodialysis, failure of an existing vascular access site may necessitate urgent central venous catheter placement. Herein, we presented a 65-year-old male patient with chronic kidney disease who presented to the emergency department for dialysis. Following evaluation, the patient was admitted to the emergency angiography unit after a carotid artery injury was detected. Extravasation was detected in the carotid artery during the procedure. The carotid artery injury was successfully managed through endovascular stent placement. No extravasation was observed on the control radiograph. Although arteriovenous fistulas have many advantages, some patients may require dialysis catheters.

Keywords: Carotid artery, computed tomography angiography, extravasation, hemodialysis catheter.

Central venous catheterization is a frequently required procedure in patients undergoing chronic hemodialysis. Although arteriovenous fistulas are the preferred method for vascular access, complications or failure of the existing access route may necessitate the use of central venous catheters. The right internal jugular vein is the most commonly used site for catheterization. However, the femoral veins may be used in emergency situations, or in cases where the internal jugular vein is occluded or there is an intracardiac thrombus.^[1] In emergency settings, femoral vein catheterization is often preferred due to the absence of risks such as hemothorax and pneumothorax. Nevertheless, because the internal jugular vein is considered a cleaner site compared to the femoral vein, it carries a lower risk of catheter-related infections. Regardless of the access site, close monitoring is recommended for all patients, as the procedure is invasive.^[2] In this study, we presented the complications that occurred during catheter insertion in a patient with chronic kidney disease, along with the interventions we performed.

and a previous colectomy for a colorectal tumor was admitted to the emergency department with complaints of diarrhea. The patient was under the ongoing care of both a cardiologist and a nephrologist and was receiving regular hemodialysis sessions for chronic renal failure. The patient was hypotensive upon arrival at the emergency department. The cardiology department was consulted to rule out acute coronary syndrome, and troponin levels were monitored, which ultimately excluded the diagnosis of acute coronary syndrome. Following the results of the tests, the patient was admitted to the internal medicine service with a preliminary diagnosis of prerenal acute renal failure. A consultation with the nephrology clinic was requested; however, emergency hemodialysis could not be initiated due to the patient's hypotensive condition (98/67 mmHg).

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CASE REPORT

A 65-year-old male patient with a history of chronic hypertension, chronic kidney disease,

On physical examination, the Glasgow Coma Scale score was 15, with the patient being conscious, clear, coherent, and oriented. Respiratory sounds were diminished on the left side and were normal on the right. Written informed consent was obtained from the patient.

The abdomen was soft, with no signs of defense or rebound tenderness. Bowel sounds were hyperactive. The patient appeared cachectic and dehydrated. The patient's colostomy was functioning, and diarrhea was present with accompanying gas discharge. Neurological examination was normal, and muscle strength was 5/5 bilaterally in both the upper and lower extremities. The patient was monitored in the internal medicine ward and subsequently discharged. However, due to the need for hemodialysis, the patient was readmitted to the emergency department for central venous catheter insertion.

Following insertion of a dialysis catheter through the right internal jugular vein, the patient's general condition deteriorated. Thoracic computed tomography angiography was performed, and our team was subsequently consulted (Figures 1, 2). The patient and investigations were evaluated urgently by our team and the thoracic surgery team. The patient was taken to the emergency angiography unit. After sterile preparation and local anesthesia, a 6F sheath was inserted into the right femoral artery under ultrasound guidance. A 0.035-inch hydrophilic wire was then advanced with vertebral catheter support.

Imaging was performed, and a wire was inserted into a temporary catheter in the right internal jugular vein. Additional imaging was conducted as the catheter was withdrawn. It was observed that the catheter had exited the jugular vein and inadvertently punctured the right carotid artery. Extravasation from the right carotid artery was noted (Figure 3). The catheter, which had been mistakenly inserted into the carotid artery, was repositioned back to its original location and secured. Subsequently, a temporary dialysis catheter was successfully placed through the right femoral vein. The patient was monitored with further investigations, and the procedure was completed without complications. For additional procedures, the patient was re-evaluated. Initially, a sternotomy extending to the right carotid region was considered

to ensure thorough exploration. However, due to the patient's poor general condition and the high surgical risk, the decision was made to proceed with angiography and endovascular intervention instead. The patient was transferred to the angiography laboratory, where, following sterile draping and administration of local anesthesia, a sheath was inserted into the left femoral artery through a puncture guided by ultrasonography. A 0.035-inch hydrophilic wire was introduced through the vertebral catheter, followed by control imaging. Finally, a pigtail catheter was placed to complete the procedure. The catheter in the right jugular vein was withdrawn and an 8×60 mm Cover Wall

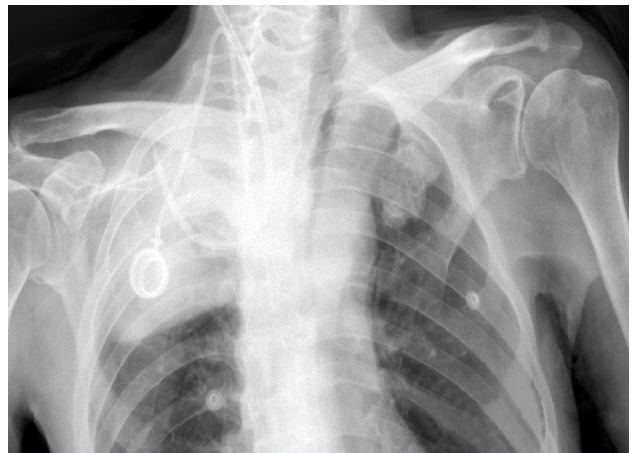


Figure 1. Chest radiograph demonstrating interposition of the right dialysis catheter.

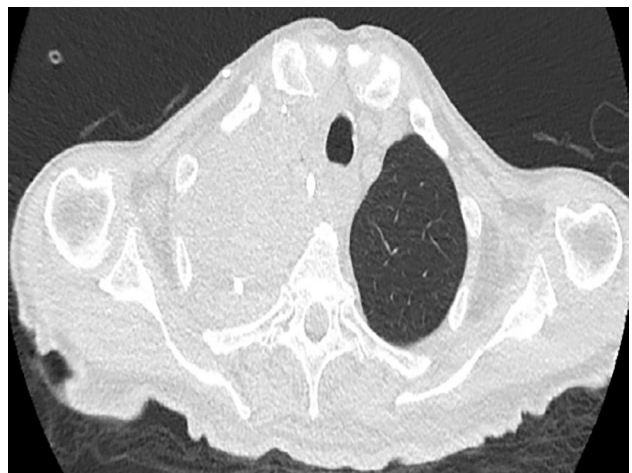


Figure 2. Computed tomography angiography demonstrating right hemothorax and contrast accumulation in the right pleural cavity.

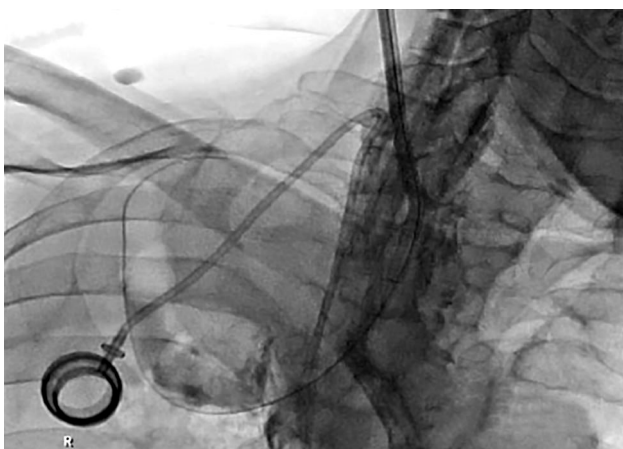


Figure 3. Extravasation detected during angiography imaging. The catheter exits beyond the carotid artery.



Figure 4. Cover Wall stent placement in the proximal part of the right carotid artery.

stent (Carotid Wallstent Monorail Endoprosthesis, 8×38 mm; Boston Scientific, Marlborough, MA, USA) was placed in the proximal segment of the right common carotid artery. Control imaging was performed and no extravasation was observed. The procedure was terminated without complications (Figure 4). The patient had an uneventful postoperative course and was discharged in good general condition after a week of follow-up.

DISCUSSION

Vascular access for dialysis catheters in chronic hemodialysis patients remains a challenging issue,

often leading to significant complications. While arteriovenous fistulas offer numerous benefits, dialysis catheters may still be necessary for some patients. The right internal jugular vein should be the first choice for venous catheter placement.^[3] However, complications such as venous thrombosis, arterial puncture, hemothorax, and pneumothorax can arise when catheters are placed via the subclavian vein.^[4] In cases of jugular vein thrombosis, infection at the catheter insertion site, lesions that may obstruct catheter placement, or the presence of intracardiac thrombus, the femoral vein can be considered an alternative access point. Although the femoral site is generally cleaner, the jugular region remains technically challenging for puncture. Hemothorax, a condition that leads to hemodynamic disturbances, is typically caused by catheter extravasation. This is more common with temporary catheters than with permanent ones due to the rigid structure of temporary catheters. It is detected by the absence of blood from the catheter or extravasation of contrast material given by imaging methods. In our case, extravasation was observed on computed tomography. According to the literature, in case of damage to the carotid arteries, a classic approach is used for better visualization of the vessels. This approach is performed by an incision parallel to the anterior edge of the midclavicular mastoid muscle. This allows timely access to the carotid arteries and the necessary interventions to eliminate bleeding. In such emergency situations, specifically in our case, this approach could be used to ensure better and timely visualization of the arteries. However, when choosing the treatment tactics, the severe general condition of the patient expressed by unstable hemodynamics was taken into account. Since the patient had a significant concomitant disease and unstable hemodynamics, we considered endovascular intervention with angiography more appropriate. In the educational literature and in scientific articles, the approach to the treatment of such complications is rarely described. The reason for this may be the untimely provision of bleeding control. However, the clinical approach and tactics of treating these complications should be based on the general condition of the patient.

In conclusion, vascular access for chronic hemodialysis remains a significant clinical challenge due to the risk of serious complications. Although

the internal jugular vein is generally the preferred site, alternative access via the femoral vein may be necessary in certain cases. Potential complications include thrombosis, hemothorax, and catheter extravasation. In the presented case, due to the patient's hemodynamic instability, an endovascular approach with angiographic guidance was selected. Ultimately, the choice of treatment strategy should be based on the patient's overall clinical condition.

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A novel approach for lower extremity malperfusion in type A aortic dissection: A case report

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ABSTRACT

Lower extremity malperfusion (LEM) is a severe complication of type A aortic dissection, often leading to ischemia and increased mortality. Optimal management remains debated, with limb-first and aortic dissection-first approaches under consideration. A 53-year-old male presented with syncope and signs of type A aortic dissection extending from the ascending aorta to the iliac bifurcation, causing dynamic LEM. To manage LEM while addressing the dissection, temporary distal perfusion was achieved using a 10F catheter connected to the femoral artery cannulation line during surgery. A Bentall procedure with hemiarch replacement was carried out (cardiopulmonary bypass time: 229 min). Postoperatively, the right lower extremity pulses were restored, and ischemia resolved without sequelae. Temporary perfusion via a central catheter from the cardiopulmonary bypass line offers a simple and effective solution to manage LEM during aortic dissection repair, potentially reducing ischemic complications. This approach may serve as a bridge to definitive repair, particularly in time-sensitive scenarios.

Keywords: Cardiopulmonary bypass, lower extremity ischemia, type A aortic dissection, vascular surgical procedures.

Aortic dissection is a life-threatening condition often complicated by branch vessel malperfusion, causing ischemia in the central nervous system, visceral organs, or extremities, posing significant therapeutic challenges.^[1] Malperfusion occurs in up to 40% of cases, increasing risks of amputation, mortality, and poor outcomes. Malperfusion is classified as static, dynamic, or both. Dynamic malperfusion results from hemodynamic forces where the dissection flap obstructs a branch vessel's orifice, while static malperfusion arises from false lumen thrombosis compressing the true lumen. Blood pressure control may restore circulation in dynamic malperfusion, but intervention is required if ineffective; static malperfusion always necessitates intervention. Rapid correction of malperfusion is critical, and choosing between a limb-first or aortic dissection-first approach impacts outcomes. Acute end-organ ischemia requires urgent reperfusion to maximize survival.^[1] However, the optimal strategy for lower extremity malperfusion (LEM) in dissection remains unclear, and amputation rates may be underreported.^[1] Traditional interventions include extra-anatomic bypasses (e.g., femoro-femoral, axillo-femoral) or surgical

fenestration, while less invasive techniques such as stent grafting and endovascular fenestration have been used since the 1990s.

This case report described a novel strategy for managing LEM in type A aortic dissection by providing temporary perfusion during dissection repair, minimizing ischemic complications.

CASE REPORT

A 53-year-old male presented to the emergency department with syncope and limb pain. Physical examination revealed left-sided ptosis and absent pulses in the right lower extremity, which was cold and pale. Echocardiography showed severe aortic

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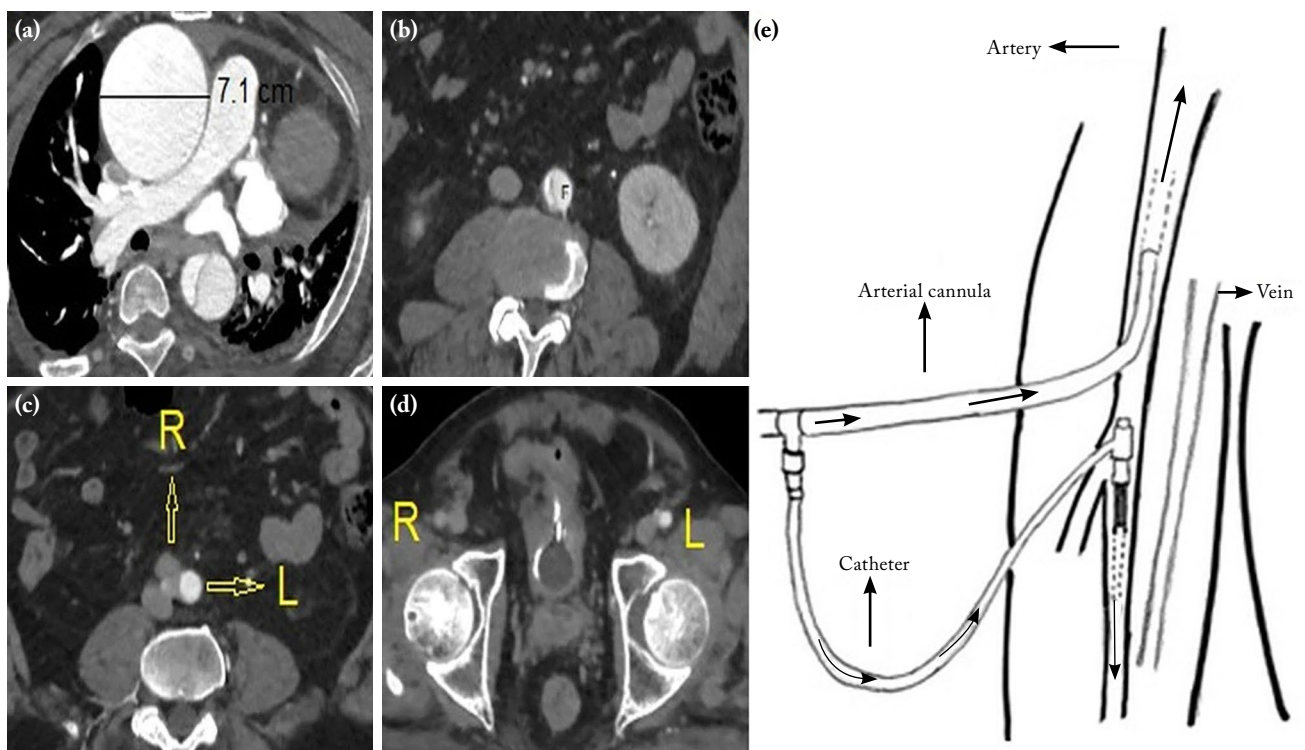


Figure 1. (a) Axial contrast-enhanced CT scan of the ascending aorta showing type A dissection. (b) Coronal CT showing reduced true lumen area in the descending aorta. (c) Axial CT at the iliac bifurcation showing false lumen dominance. (d) Contrast in left femoral artery (absent in the right). (e) Schematic diagram of femoral and subclavian cannulation with 10F catheter.

CT: Computed tomography.

insufficiency. Computed tomography (CT) confirmed a DeBakey type A dissection (Figures 1a-d). At the celiac artery origin, the false lumen dominated the aortic cross-sectional area, with increasing dominance distal to the renal arteries. At the iliac bifurcation, the false lumen occupied the entire area (Figure 1c). The left iliac artery (false lumen-originating) showed contrast filling, but the right common iliac, external iliac, and proximal femoral arteries (true lumen-originating) exhibited no contrast, indicating dynamic malperfusion (Figure 1d). Written informed consent was obtained from the patient.

Surgical procedure

Arterial cannulation was established in the right subclavian artery for cerebral perfusion and in the right femoral artery for retrograde true lumen perfusion. A 10F catheter was connected to the femoral artery cannulation line, with catheterization distal to the cannulation site to provide distal perfusion to the right lower extremity (Figure 1e).

This enabled simultaneous retrograde flow from femoral cannulation and antegrade flow via the 10F catheter. After restoring extremity perfusion, a Bentall procedure with a no. 21 mechanical valved conduit and hemiarch replacement were performed after median sternotomy. Cardiopulmonary bypass (CPB) time was 229 min, cross-clamp time was 146 min, and total circulatory arrest time was 20 min. Postoperatively, pulses returned in the right lower extremity, with complete resolution of ischemia and no sequelae. No ischemia-reperfusion complications, such as severe metabolic acidosis, occurred. The patient stayed in the intensive care unit for eight days due to respiratory issues and was discharged after 15 days with no residual deficits. Follow-up CT showed contrast filling in both femoral arteries (Figure 2).

DISCUSSION

Lower extremity malperfusion in acute type A aortic dissection remains a complex clinical entity with

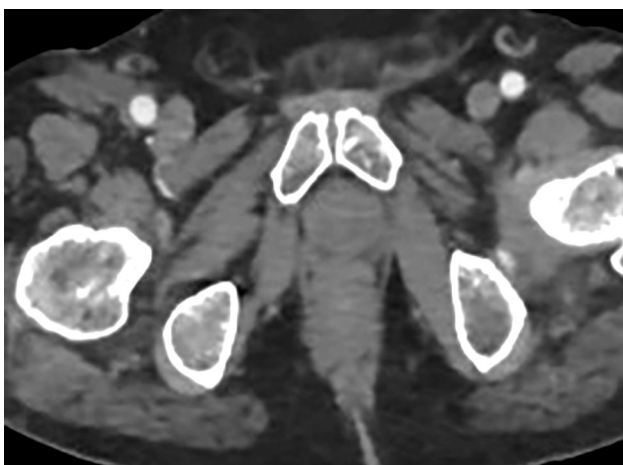


Figure 2. Postoperative computed tomography showing restored bilateral femoral perfusion.

significant prognostic implications. The therapeutic dilemma centers around whether to prioritize limb revascularization or central aortic repair, as delayed perfusion can exacerbate ischemic injury, yet postponing dissection repair may lead to fatal complications. Plotkin et al.^[1] reported increased early failure rates in patients undergoing limb-first interventions compared to those receiving immediate aortic repair, while Charlton-Ouw et al.^[2] noted that one-third of LEM cases required additional interventions after aortic surgery.

In the present case, the patient exhibited dynamic malperfusion of the right lower extremity due to collapse of the true lumen at the iliac bifurcation. Arterial cannulation was achieved via the right femoral artery to access the true lumen. To preserve perfusion to the distal limb during Bentall procedure, a 10F catheter was introduced distal to the femoral cannulation site and connected to the CPB line. This allowed for simultaneous antegrade and retrograde flow during systemic circulation support, maintaining limb perfusion throughout the surgical period.

This approach is conceptually related to distal perfusion techniques commonly used in extracorporeal membrane oxygenation patients to prevent limb ischemia^[3] but has been adapted here to the context of acute aortic dissection surgery. The advantage of this technique lies in its simplicity, timeliness, and compatibility with emergent operative settings without the need for additional surgical exposure or delayed reperfusion.

Postoperatively, the patient did not require any further intervention for the lower extremity. Ischemia resolved completely without evidence of neurologic or muscular sequelae. Although metabolic acidosis occurred transiently following reperfusion, it responded to standard medical management. These outcomes suggest that intraoperative maintenance of distal perfusion may contribute to mitigation of ischemia-reperfusion injury, an effect previously highlighted in the context of malperfusion management.^[4,5]

The strategy employed aligns with evolving perspectives on individualized cannulation techniques in aortic dissection. Xia et al.^[6] emphasized the utility of double arterial cannulation in providing both cerebral and distal organ perfusion, particularly in complex cases with compromised true lumen flow. While our approach does not involve formal double arterial cannulation in the classic sense, the use of a temporary distal perfusion line achieves a similar goal, ensuring effective systemic and peripheral circulation during the critical phases of aortic repair.

In conclusion, LEM in aortic dissection increases mortality and morbidity, and its optimal management remains unresolved. Our novel approach of temporary perfusion via a 10F catheter from the CPB line during dissection repair offers a simple, effective method to address LEM while enabling prompt dissection repair. This strategy may reduce ischemic complications in time-sensitive settings, warranting further investigation.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Magnetic resonance angiography diagnosis of late-onset dysphagia due to arteria lusoria

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Anatomic variations of the great vessels, particularly involving the subclavian artery, are important to recognize due to their potential impact on surgical, endovascular, and diagnostic procedures.^[1,2] Arteria lusoria is the most common aortic arch anomaly also known as aberrant right subclavian artery in a pathology where brachiocephalic trunk is absent and four large arteries arise from the arch of the aorta: the right common carotid artery (CCA), the left CCA, the left subclavian artery, and the final one with the most distal left-sided origin, the right subclavian artery. This vessel travels to the right arm, crossing the middle line of the body and usually passing behind the esophagus. If the artery compresses the esophagus, it may produce a condition called dysphagia lusoria. The incidence is reported to be 0.2 to 1.7% in population. Frequently, the arteria lusoria arises from an aortic arch diverticulum at the proximal descending aorta, first described by Kommerell.^[3]

In this report, we present a rare case of an anomalous right subclavian artery originating posteriorly from the aortic arch with accompanying vascular stenosis diagnosed in an adult.

A 67-year-old male patient was hospitalized and intubated by the anesthesia team with preliminary diagnoses of respiratory distress and general condition deterioration and pneumonia. His past medical history was unremarkable, and there was no history of trauma or significant cardiovascular events. Subsequently, a magnetic resonance imaging (MRI) was performed, which revealed an anomaly of the right subclavian artery and aorta. A contrast-enhanced magnetic resonance (MR) angiography was, then, conducted to confirm the diagnosis. Although the MRI images

showed significant compression on the esophagus and mild compression on the trachea, the patient had no prior history of shortness of breath or difficulty swallowing.

Contrast-free MR angiography of the carotid and cervical arteries was performed. The imaging findings revealed right subclavian artery originating from the posterior-inferior aspect of the aortic arch and passing posterior to the esophagus and trachea (Figure 1a, b, d), suggesting an aberrant subclavian artery (arteria lusoria) variant. The proximal right subclavian artery was dilated, measuring approximately 27 to 28 mm in diameter, and exhibited a distinct bulging appearance with no significant calcification (Figure 1a, b). Both CCAs displayed narrow diameters at their origin (approximately 22 mm), indicative of potential vascular narrowing. Left internal carotid artery (ICA) showed a segmental narrowing of approximately 5 mm with a 40% diameter reduction in the proximal segment (Figure 1a, b). Segmental hypoplasia of the right vertebral artery was observed, and a short segment stenosis was noted in the vertebrobasilar system (Figure 1c).

The patient was intubated and hospitalized in intensive care unit for 15 days and died due to pneumonia and sepsis. Written informed consent was obtained from the patient.

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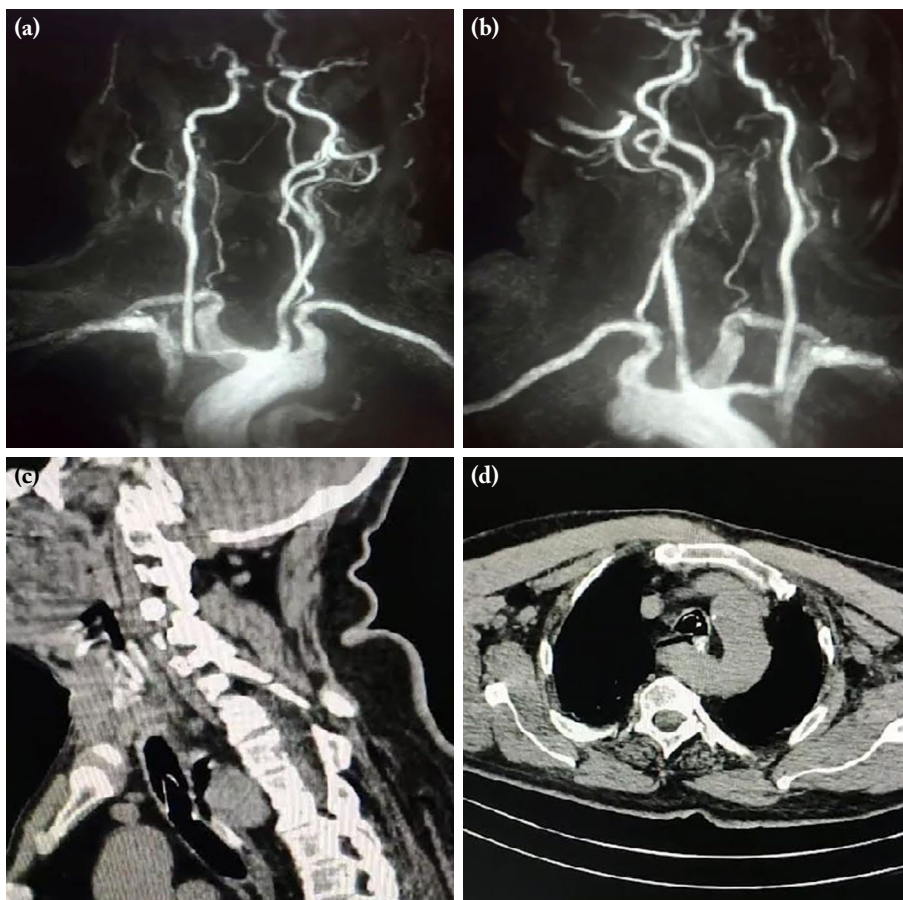


Figure 1. (a-c) The aberrant course of the right subclavian artery, stenosis in the left internal carotid artery and hypoplasia of the right vertebral artery. (d) The course of the aberrant subclavian artery and aorta demonstrating compression on the esophagus and trachea.

Anomalies in the origin and course of the subclavian artery, particularly arteria lusoria, are typically asymptomatic but may manifest with symptoms due to esophageal or tracheal compression or associated vascular pathologies.^[1,2,4] In this case, the aberrant course of the right subclavian artery, combined with significant stenotic lesions in the cervical arteries, underscores the importance of accurate imaging for both diagnosis and management.^[5,6]

In conclusion, the presence of luminal narrowing in the ICAs and CCAs raises concerns about cerebrovascular insufficiency, particularly in light of the patient's symptoms. The findings also highlight the utility of MR angiography and MRI imaging in non-invasively identifying vascular anomalies without the risks. The anomalous origin and course of the right subclavian artery, coupled with stenotic changes in the

cervical arterial system, necessitate a tailored approach to management, potentially including surgical or endovascular intervention if symptoms persist or worsen.

Patient Consent for Publication: A written informed consent was obtained from the patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Comment on: The utility of vitamin D levels in predicting the severity of coronary artery disease in obese patients

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I read with interest the article titled “The utility of vitamin D levels in predicting the severity of coronary artery disease in obese patients” by Candemir et al.,^[1] published in the journal Cardiovascular Surgery and Interventions. This cross-sectional study investigates the relationship between vitamin D (25-hydroxy [OH]D, 25[OH]D) levels and the severity of coronary artery disease (CAD) in obese patients undergoing coronary angiography due to stable angina pectoris, using the SYNTAX score. The data obtained from the study indicate that in obese patients with vitamin D deficiency, the severity of CAD increases in relation to higher SYNTAX scores. However, I believe several points need to be addressed.

I believe it is necessary to provide information about the patients undergoing coronary angiography due to stable angina pectoris, such as their previous coronary angiography history, stent history, and current medical treatments. Additionally, the effects of current treatments on vitamin D levels should also be considered.

There is extensive literature on the effects of statins, which are frequently used in the treatment of CAD, on vitamin D levels. Therefore, I believe the current medical treatments of the patients should also be taken into consideration.

Additionally, climate and sun exposure time significantly contribute to vitamin D production. Hence, I believe that these findings could be further expanded through multicenter studies examining potential connections between climate, sun exposure time, and vitamin D production. Additionally, as the authors have also mentioned, I believe that increasing the number of patients will lead to more valuable data.

In conclusion, the study by Candemir et al. suggests that more severe CAD is observed in obese individuals. The fact that vitamin D deficiency may be an independent predictor of CAD severity in this population is very valuable. I congratulate the authors and look forward to future research on this topic and hope that the authors will consider my suggestions in their future work.

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Response to the comment on: Comment on the utility of vitamin D levels in predicting the severity of coronary artery disease in obese patients

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We thank the author for their interest and comments about our study, which demonstrated that vitamin D deficiency is associated with higher SYNTAX scores, an indicator of CAD severity.^[1]

The author^[2] states that more information is needed about patients' various previous cardiac diseases and treatments. We excluded patients with any history of cardiovascular disease from the study. None of the patients were using any treatment that would affect vitamin D levels. In addition, patients who used antilipidemic agents within the last six months were also excluded from the study.

The author emphasized the importance of climate and sun exposure time on vitamin D synthesis. We also acknowledge these factors; however, since all the patients we included in the study lived in similar areas, we do not believe that it significantly affected the results of the present study. However, we agree that studies to be conducted in different regions and even different countries will shed more detailed light on this subject.

As the author stated, it would have been better if we could have included more patients in the study. However, due to our strict inclusion criteria, we could only reach a limited number of patients, and this was acknowledged in the limitations.

In conclusion, we demonstrated a significant association between lower serum vitamin D levels and higher SYNTAX scores. Further larger studies are needed to confirm our findings.

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Comment on: Changes in hand grip strength and associated factors after transradial coronary intervention: A longitudinal study

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I read with interest the article titled “Changes in hand grip strength and associated factors after transradial coronary intervention: A longitudinal study” published recently in the journal of Cardiovascular Surgery and Interventions by Erbay et al.^[1] The study is an important and timely study in terms of emphasizing the complications that may occur after transradial coronary intervention.

The data presented in the study clearly demonstrate the situations that should be considered during transradial coronary intervention. In this sense, the suggestions presented to increase the success of transradial coronary intervention are quite important. However, I believe there are some points that need to be addressed in this study.

Although it is unlikely that carpal tunnel syndrome (CTS) is solely due to the transradial procedure, it is possible that the functional response to the prolonged application of a radial artery pressure device after the procedure, as well as trauma-induced edema, may have contributed to the development of CTS or worsened preexisting CTS.^[2] This may affect the median nerve and cause a decrease in hand grip strength. On the other hand, conditions such as trauma-induced hematoma and inflammation-induced wrist swelling may cause a decrease in hand grip strength.^[3]

Therefore, when the optimal number of specialists is provided according to the population, I believe the reasons for referrals to the wrong department will be better understood.

In conclusion, the study by Erbay et al.^[1] provides valuable information by addressing an important issue in transradial coronary intervention. I eagerly

await further research in this area and hope that the authors will consider these suggestions in their future studies. Thank you for the opportunity to provide feedback on this important study.

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