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Are preoperative neutrophil/lymphocyte, platelet/lymphocyte, and platelet/neutrophil ratios markers in new-onset atrial fibrillation after coronary artery bypass grafting?

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ABSTRACT

Objectives: This study aims to investigate the predictive value of platelet/neutrophil ratio (PNR) as a marker for postoperative atrial fibrillation (POAF) in addition to neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) measured in the preoperative period in patients who underwent coronary artery bypass grafting (CABG).

Patients and methods: The data of a total of 122 patients (89 males, 33 females; mean age 63.2±9.19, range, 41 to 86 years) who underwent isolated CABG in our clinic and had no prior atrial fibrillation history between May 2018 and February 2020 were reviewed retrospectively. The patients were divided into two groups as those with and without POAF. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated.

Results: Postoperative atrial fibrillation was detected in 36 of 122 patients. A significant difference was found in lymphocyte count (p=0.043), NLR (p=0.01), and PNR (p=0.048) in the patients who developed POAF. In the univariate logistic regression model, NLR was found to be an independent predictor for POAF development with 75% sensitivity, 53% specificity, 61.5% PPV, 67.9% NPV, and 64% accuracy (AUC: 0.646, p=0.01). In the POAF patients, the ROC analysis was performed to determine the diagnostic value of the PNR; however, no significant results were obtained.

Conclusion: Our study results show an independent association between baseline NLR and POAF after CABG surgery.

Keywords: Atrial fibrillation, coronary artery bypass grafting, platelet/lymphocyte ratio, platelet/neutrophil ratio, neutrophil/lymphocyte ratio.

The most common rhythm disorder after cardiac surgery is atrial fibrillation (AF).[1] The first three-day after surgery is the period with the highest incidence of postoperative atrial fibrillation (POAF).[2] In particular, in this period, although the etiology of POAF is multifactorial, one of the most important causes is the ongoing inflammatory and oxidative changes.[3] Neutrophils are an indicator of activated non-specific inflammatory response, and lymphopenia is an indicator of physiological stress and poor general health.[4] It has been shown that lymphocytes also regulate the immune response at all stages of progressive atherosclerosis. As the source of inflammatory mediators, platelets play an important role in the pathogenesis of AF due to their relationship with both thrombosis and inflammation.[5,6] In addition, increased platelet and decreased lymphocyte levels have been associated with poor prognosis in cardiovascular diseases.[7,8] In this context, neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have been reported as indirect indicators of systemic inflammatory response and markers for POAF in recent years.[9,10]

There is no study using the platelet/neutrophil ratio (PNR) as an inflammatory marker, not only for POAF, but also for any other field in the literature. In the present study, therefore, we aimed to investigate the predictive value of PNR as a marker for POAF in addition to NLR and PLR measured in the preoperative period in patients who underwent coronary artery bypass grafting (CABG).

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PATIENTS AND METHODS

The data of a total of 122 patients (89 males, 33 females; mean age 63.2±9.19, range, 41 to 86 years) who underwent isolated CABG in our clinic between May 2018 and February 2020 were reviewed retrospectively. Patients who had a history of AF in the preoperative period or underwent off-pump surgery, had a valve pathology, underwent combined valve-CABG, were taken to the emergency operation, had a history of hyperthyroidism, hypothyroidism, infection, autoimmune disease in the preoperative period, and patients using steroid, amiodarone, digital, synthetic hormone preparations were excluded from the study. A written consent form was obtained from each patient. The study protocol was approved by Suleyman Demirel University, Faculty of Medicine, Ethics Committee (No. 12.03.2020/78). The study was conducted in accordance with the principles of the Declaration of Helsinki.

A detailed medical history, physical examination and routine blood tests, echocardiogram, electrocardiogram, carotid Doppler ultrasound (CDUS), chest radiograms and respiratory function tests, body mass index (BMI), European System for Cardiac Operative Risk Evaluation (EuroSCORE) were performed in all patients who were scheduled for an open heart surgery. Patients who were smoking on the date of coronary angiography were evaluated as smokers. Internal medicine consultation was requested for the patients who had a previous diagnosis of diabetes mellitus (DM) and patients who did not have a diagnosis of DM, but whose fasting blood glucose was >126 mg/dL and the diagnosis of DM was confirmed. Patients who previously received antihypertensive treatment and those who had >130/85 mmHg blood pressure during clinical follow-up were considered hypertensive (HT) patients. Before the operation, the use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), β-blocker and statin history were examined. The patients on routine hemodialysis program were evaluated as patients with chronic kidney failure. All patients who had chronic pulmonary obstructive disease (COPD) were evaluated by a chest physician with pulmonary function test or by arterial blood gas examination and those who were unable to perform pulmonary function tests were evaluated with physical examination. Those with a history of myocardial infarction (MI) within the past three months were evaluated as recent MI. The patients with dyspnea symptoms even at rest were considered the New York Heart Association (NYHA) Class IV according to the NYHA congestive heart failure classification.

Biochemical and hematological parameters

Blood samples were taken after 12 h of fasting. Complete blood counts, which included total white blood cells (WBCs), neutrophils, lymphocytes, and platelets were obtained using an automated blood counter, Mindray BC 6800 (Mindray, Shenzhen China). The NLR was calculated as the ratio of neutrophils (10^3/uL)-to-lymphocytes (10^3/uL), PLR was calculated as the ratio of platelets (10^3/uL)-to-lymphocytes (10^3/uL), and PNR was calculated as the ratio of platelets (10^3/uL)-to-neutrophils (10^3/uL) obtained from the blood samples. C-reactive protein (CRP) levels were measured using the Siemens BN II System (Siemens Medical Solution, Malvern, PA, USA), and the preoperative glomerular filtration rate (GFR) was estimated using standard methods.

Operative technique

Median sternotomy was applied to all patients under general anesthesia. Cardiopulmonary bypass (CPB) was performed using aortocaval cannulation technique in all patients following systemic heparin administration (300 IU/kg). Cardiac arrest was achieved using hypothermic, hyperkalemic blood cardioplegia, and topical hypothermia. Surgery was performed under moderate systemic hypothermia (32°C). The CPB flow was maintained at 2.2-2.5 L/min/m^2, mean perfusion pressure was maintained between 50 and 80 mmHg, and hematocrit level was maintained at 20-25% during CPB. Cardiac arrest was maintained using intermittent antegrade cold blood cardioplegia infusions. In patients who had low ejection fraction (EF), multi-vessel disease (MVD), and poor ventricular function, continuous retrograde cold blood cardioplegia was infused in addition to antegrade intermittent cold blood cardioplegia. The left internal mammary artery was used in all patients for revascularization of the left anterior descending artery. A saphenous vein graft was used for grafting other coronary arteries. Warm blood cardioplegia was given in all patients immediately before removing the cross-clamp. All proximal anastomoses were performed using side clamps. All early postoperative patient follow-ups were done in the third-degree cardiovascular surgery intensive care unit (ICU).

POAF

All patients were monitored in the ICU after surgery with a five-lead monitoring system Philips IntelliVue MX800 (Philips, Boeblingen, Germany) using the standard lead II configuration. After discharge from the ICU, the patients were followed six to eight times daily in the ward. Following surgery, subsequent 12-lead electrocardiograms were daily obtained from each patient until discharge and also, if a patient manifested with symptoms of palpitations or an irregular pulse, a 12-lead electrocardiography Mindray Bene Heart R12 (Shenzhen Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, China) was performed to diagnose the arrhythmia. New-onset POAF was described as AF according to the established Society of Thoracic Surgeons definition occurring during hospitalization after CABG in a patient with no history of AF. Episodes of AF were treated according to clinical routines which included pharmacological interventions with intravenous amiodarone or, if contraindicated, with an oral β-blocker (metoprolol) and/or with electrical therapies such as cardioversion.

Statistical analysis

Power analysis and sample size calculation were performed using the G*Power version 9.1.2 (University of Düsseldorf, Düsseldorf, Germany). In the power analysis performed by evaluating the frequency of POAF development in the literature, the sample was calculated by taking the power value 85% and the effect size 0.75. Accordingly, the sample size for the case group was determined to be 30 patients who developed POAF and 70 patients who did not develop POAF.

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were presented in number and frequency, while continuous variables were expressed in mean ± standard deviation (SD) or median

Table 1
Baseline demographic and clinical characteristics of patients

	POAF negative (n=86)			POAF positive (n=36)			
Characteristic	n	%	Mean±SD	n	%	Mean±SD	*p*
Sex							0.223
Male	60	69.8		29	80.6		
Female	26	30.2		7	19.4		
Diabetes mellitus							0.799
No	38	44.2		15	47.7		
Yes	48	55.8		21	58.3		
Considered hypertensive							0.434
No	52	60.5		19	52.8		
Yes	34	39.5		17	47.2		
COPD							0.921
No	51	59.3		21	58.3		
Yes	35	40.7		15	47.7		
Smoker							0.420
No	66	76.7		30	83.3		
Yes	20	23.3		6	16.7		
Recent myocardial infarction							0.183
No	62	68.1		20	55.6		
Yes	29	31.9		16	44.4		
Age (year)			62.4±9.6			64.5±9.2	0.364
Number of bypasses (n)			3.2±0.8 (3; 1; 5)			3.1±0.8 (3; 1; 5)	0.661
Body mass index (kg/m^2)			28.7±4.3			29.9±4.4	0.122
Cardiopulmonary bypass time (min)			114.7±35.4			112.7±30.4	0.713

POAF: Postoperative atrial fibrillation; SD: Standard deviation; COPD: Chronic pulmonary obstructive disease.

(min-max). The consistency of continuous variables to normal distribution was tested by Kolmogorov-Smirnov test. In general, the variables were not distributed normally. Therefore, the Mann-Whitney U test was performed for the comparison of two independent groups, and Monte Carlo exact chi-square (χ^2) test was used to determine the correlation between the categorical variables. A prospective progressive

Table 2
Patient data

	POAF negative (n=91)			POAF positive (n=36)			
Characteristics	n	%	Mean±SD	n	%	Mean±SD	*p*
NYHA Class IV							0.841
No	83	96.5		35	92.7		
Yes	3	3.5		1	2.8		
Beta-blocker							0.186
No	12	14.0		2	5.6		
Yes	74	86.0		34	94.4		
Statin							0.345
No	73	84.9		28	77.8		
Yes	13	15.1		8	22.2		
ACEI/ARB							**0.005***
No	71†	82.6		21‡	58.3		
Yes	15†	17.4		15‡	41.7		
LIMA							0.523
No	1	1.2		1	2.8		
Yes	85	98.9		35	97.2		
Ejection fraction (%)			54.2±9.4			53.9±9.0	0.813
GFR (mL/mn)			85.9±15.5			80.6±16.7	0.132
EuroSCORE			1.5±1.1 (1.13; 0.5; 7.23)			1.6±1.3 (1.25; 0.50; 7.65)	0.613
LA diameter (mm)			36.5±4.1			37.7±5.7	0.442
CRP (mg/dL)			1.1±1.5 (0.44; 0.30; 6.90)			1.0±1.1 (0.59; 0.30; 4.19)	0.753
X-clamp (min)			67.2±21.9			65.8±21.0	0.651
Hemoglobin (mg/dL)			13.4±1.6			13.5±1.5	0.395
White blood cell			7.6±2.0			7.9±2.1	0.571
Neutrophil (10^3/µL)			4.5±1.4			5.1±1.8	0.132
Lymphocytes (10^3/µL)			2.2±0.8			1.9±0.5	0.043*
Monocytes (10^3/µL)			0.5±0.2			0.5±0.2	0.659
Platelet			243.4±72.2			236.8±66.4	0.509
NLR			2.2±0.8			2.7±1.1	0.010*
PLR			116.5±33.7			130.3±45.9	0.315
PNR			58.5±21.9			51.7±20.9	0.048*
Neutrophil/CRP			8.9±5.8			8.7±5.9	0.954
Lymphocytes/CRP			4.8±3.7			4.1±2.9	0.585
Platelet/CRP			480.5±293.5			460.1±324.7	0.676

POAF: Postoperative atrial fibrillation; SD: Standard deviation; NYHA: New York Heart Association; ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LIMA: Left internal mammary artery; GFR: Glomerular filtration rate; LA: Left atrium; CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; PNR: Platelet/neutrophil ratio; † Mann-Whitney U test. ‡ Chi-square test; * $p<0.05$.

univariate logistic regression model was constructed to determine the factors affecting development of POAF. The receiver operating characteristic (ROC) curve analysis was applied for proportional scale variables which were found significant among the contributing factors. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated according to the calculated cut-off value. Type-I error value was taken as 5% in the whole study. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 122 patients, 29.5% (n=36) developed POAF. More than half of the cases included in the study had DM (56.6%), almost half had HT (41.8%) and COPD (41.0%). While 21.3% of the patients were smokers, 36.9% of them had a recent history of MI. While the majority of patients were using β-blockers (88.5%), statin use was low (17.2%) and ACEI use was 24.6% (Table 1).

Various clinical features and measurement values were compared between the patients with and without POAF. The values measured in demographic features and clinical features did not significantly differ between the groups. Age, BMI, WBC, and PLR values were higher in the patients who developed POAF. The CPB time, EF, GFR, cross-clamp time, and platelet values were lower in the patients who developed POAF, although it did not reach statistical significance. Only in hematological measurements, the lymphocyte count (p=0.043), NLR (p=0.010) and PNR (p=0.048) and ACEI/ARB use (p=0.005) significantly differed in the patients with POAF. The mean lymphocyte count, which was significantly lower in the POAF group, was found to be 1.94±0.54 10^3/μL in the patients who developed POAF, while it was 2.23±0.82 10^3/μL in the patients without AF. The mean NLR value was found to be 2.73±1.10 in the patients with POAF and 2.15±0.81 in the patients without POAF. The mean PNR decreased in the patients with POAF (51.72±20.84). The ratios of neutrophil, lymphocyte, and platelet counts-to-CRP values were determined. Although the rates obtained using CRP were found to be lower in the patients who developed POAF, there was no significant difference in predicting the development status of POAF (Table 2).

A univariate logistic regression model was created considering developing POAF as a dependent category and not developing it as the reference category. Drug use, comorbid diseases, demographic features, and biochemistry measurements were included in the prospective model created by the forward likelihood ratio (LR) method. The goodness-of-fit results of the model obtained as a result of the second stage were found to be significant (omnibus test χ^2=15.29, p<0.001; -2LL=132.72, Nagelkerke R^2=0.168; Hosmer-Lemeshow χ^2=15.53, p=0.052). Only two variables significantly contributed to the model. It was calculated that the effect of NLR was positive and the effect of ACEI/ARB use was negative. The odds ratio (OR) was 1.833 (p=0.07) for NLR and 0.335:2.985 (p=0.017) for ACEI/ARB use (Table 3).

The ROC analysis was performed to test the success of NLR values in predicting POAF development (Figure 1). The area under the curve (AUC) was found to be significant (AUC=0.649; p=0.010). In the calculation, the cut-off value was calculated as 2.04. Accordingly, the differential diagnosis rates (95% confidence interval [CI]) were calculated as follows: sensitivity: 75% (65.3-83.1%), specificity= 53% (42.7-63.1%), PPV= 61.5% (55.7-66.9%), NPV= 67.9% (59.1-75.7%), and accuracy= 64% (56.9-70.6%).

Table 3
Correlation analysis results

		Nagelkerke R^2=0.168		Hosmer & Lemeshow χ^2=15.531 (p=0.052)
Factors	Model	Beta	p	OR (95% CI)
NLR		0.606	0.007*	1.833 (1.183-2.838)
ACEI/ARB	Use	-1.093	0.022*	0.335 (0.137-0.821)
				2.985 (1.218-7.299)

OR: Odds ratio; CI: Confidence interval; NLR: Neutrophil/lymphocyte ratio; ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

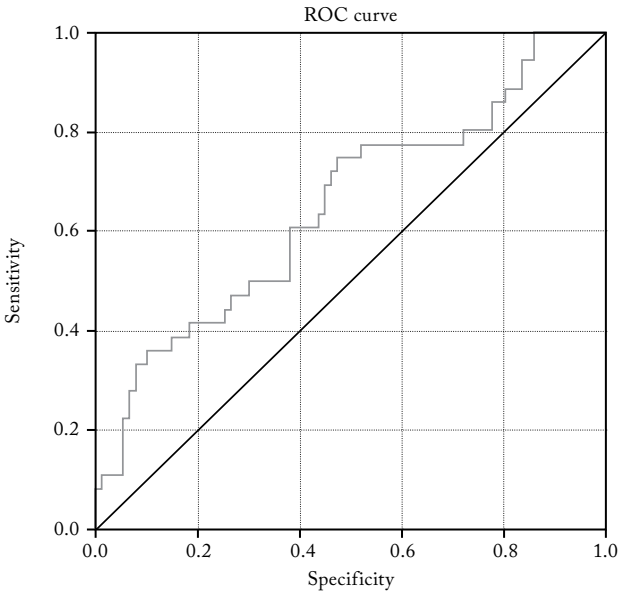

Figure 1. Receiver operating characteristic (ROC) of neutrophil-lymphocyte ratio in postoperative atrial fibrillation.

In the POAF group, the ROC analysis was performed to determine the diagnostic value of the PNR which was found to be significantly low (AUC=0.575, p=0.244) although the results were not found to be significant in the ROC analysis.

DISCUSSION

In this study, a high preoperative NLR and low preoperative PNR were evaluated as risk factors for the development of new-onset POAF in patients undergoing CABG. On the other hand, lymphocyte counts, and the ACEI/ARB use were higher in the patients who were in normal sinus rhythm.

The most common arrhythmia after CABG is AF and POAF can be seen in 15 to 40% of cases following isolated CABG.[1] Atrial fibrillation can cause complications such as heart failure, thromboembolism, cerebrovascular occlusive events, and renal insufficiency. Also, it is one of the leading causes of mortality after CABG itself and, due to morbidities caused by AF, many patients have prolonged hospital stays and prolonged hospitalization increases the cost per patient.[11] New-onset POAF is associated with many factors such as age, male sex, DM, HT, recent MI, heart failure, obesity, and left atrial size.[1,10] In our study, although age and BMI measurements were found to be higher in the POAF group, no statistically significant difference was found between those with and without POAF.

The relationship between AF following after cardiac surgery and preoperative inflammatory markers has been evaluated in many studies and demonstrated by inflammatory cell infiltration and interstitial fibrosis observed in the atrial tissues of patients developing AF. The link between oxidative stress following after cardiac surgery, complex inflammatory response.[12,13] caused by the effect of cellular inflammation, interleukin 6 and 8, increased WBC count, CRP levels, and AF development has been previously shown.[14-16] In our study, although WBC counts were found to be higher in the patient group who developed POAF, it was not statistically significant. In addition, there was no significant difference in the CRP levels in the patients with or without POAF.

The WBC count and its subtypes have been found to be markers of inflammation in various cardiovascular diseases.[4] Neutrophils represent activated non-specific inflammation.[4] In addition, neutrophil activation during CPB causes perioperative myocardial damage and, subsequently, reperfusion injury.[4,17,18] Decreased lymphocytes are associated with poorer general health, increased physiological stress, and depressed immune response.[4] Platelets play an important role in inflammation and thrombosis by secreting various mediators.[6] Therefore, we examined WBC subtypes in our study. We found lower lymphocyte counts in the patients with POAF compared to those without POAF (p=0.043). However, we found no significant difference in the neutrophil, platelet, and basophil counts between the groups. In recent years, the NLR, PLR, and non-specific inflammatory response have been associated in many studies based on the increase in neutrophil and platelet counts and a decrease in the lymphocyte counts.[7-11,19-22]

Correlation studies between NLR and development of AF conducted by Gibson et al.[9] showed that the rate of AF development was higher in patients with a high NLR value, which is used as an inflammatory marker.[4,23] Also, in this study, preoperative NLR was independently associated with POAF with 75% sensitivity and 53% specificity.

A limited number of studies is available in the literature reporting the association between PLR and POAF after CABG surgery. Gungor et al.[10]

found a higher risk of developing POAF in patients with higher preoperative PLR. Later, this result was supported by similar studies.[24,25] In our study, we found a higher preoperative PLR in the patients with POAF. However, we found no statistically significant difference in the preoperative PLR values in the patients who did not develop POAF (p=0.315).

To the best of our knowledge, this is the first study to evaluate PNR for inflammation and AF predictability in the literature. In our study, the PNR was found to be a significantly lower predictor for POAF, although no significant results were found in the ROC analysis (AUC: 0.575, p=0.244). We believe that low PNR in patients who develop POAF can yield significant results in predicting the development of POAF. However, further large-scale studies are needed to confirm this hypothesis.

Although ACEI and ARB inhibit the renin-angiotensin system by targeting different sites in the pathway, clinical studies have shown that both drugs effectively lower blood pressure and reduce cardiovascular events.[26,27] They can modify atrial substrate, prevent inflammation and, thus, reduce the risk of AF.[28,29] A growing number of evidence suggests that ACEI and ARB can be used for AF prevention.[30,31] In our study, we found that ACEI/ARB use was protective against POAF development in the preoperative period in addition to NLR and PNR (OR=0.335).

The limitations of this study include its relatively small sample size, retrospective design, and relatively short follow-up period. Asymptomatic, short-term POAF episodes or new-onset POAF within the first month of control visit following discharge may not have been identified.

In conclusion, unlike many other inflammatory markers and bioassay, the PNR, NLR, and PLR are simple, inexpensive, and routinely reported tests as a part of complete blood count. In this study, we found an independent correlation between baseline NLR and POAF after CABG surgery. In addition, when studied in larger cohorts, the decrease in the PNR in patients who develop POAF can yield significant results in predicting the development of POAF and can be used as a marker. Nonetheless, further, large-scale, long-term, prospective studies using PNR, NLR, and PLR are required to evaluate long-term outcomes of POAF after CABG surgery.

Declaration of conflicting interests

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Comparison of prophylactic levosimendan versus intra-aortic balloon pump for off-pump coronary artery bypass grafting in patients with low ejection fraction: A randomized-controlled trial

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ABSTRACT

Objectives: This study aims to compare the efficacy and short-term clinical outcomes of levosimendan versus intra-aortic balloon pump (IABP) in patients undergoing off-pump coronary artery bypass grafting (OPCABG).

Patients and methods: This prospective, randomized-controlled study included a total of 60 patients (44 males, 16 females; mean age 60.58+5.23 years; range, 42 to 70 years) with low left ventricular ejection fraction (<25%) undergoing OPCABG between January 2019 and September 2019. The patients were divided into two groups as levosimendan (Group L) and IABP (Group B). Hemodynamic parameters were measured at prespecified time points.

Results: Hemodynamic data recorded at baseline were comparable in both groups, while cardiac index progressively increased in both groups. Although, the increase was statistically significant on multiple measures analysis of variance in both groups, no significant difference was observed at different time points. Pulmonary capillary wedge pressure decreased in both groups; however, the decline was not statistically significant. Serum lactate concentration was consistently lower in Group B compared to Group L at all time points. The heart rate, mean arterial pressure, and Vasoactive Inotropic Score (VIS) were comparable in both groups at all time points. The mean length of intensive care unit (ICU) stay was statistically significant in Group B compared to Group L.

Conclusion: The use of prophylactic levosimendan is comparable to prophylactic IABP, when hemodynamic parameters are considered. Prophylactic levosimendan is associated with a shorter length of hospital and ICU stay. Prophylactic levosimendan can be considered an alternative to prophylactic IABP in patients with low ejection fraction in whom IABP is contraindicated.

Keywords: Coronary artery bypass grafting, intra-aortic balloon pump, levosimendan, low ejection fraction, off-pump.

Off-pump coronary artery bypass grafting (OPCABG) is often complicated by hemodynamic instability, particularly in patients with left ventricular (LV) dysfunction. One of the life-threatening complications in patient with low LV ejection fraction (LVEF, <25%), is the development of perioperative myocardial dysfunction which may lead to multiple organ dysfunction in the postoperative period, and increased duration of hospitalization and mortality.[1,2]

The main challenge during OPCABG is to maintain optimum hemodynamics. It is challenging to continue the procedures off-pump. Traditionally this has been achieved by mechanical support that is by intra-aortic balloon pump (IABP) use. Levosimendan is a novel inotropic agent, which has been used in the management of acute decompensated heart failure. It acts by binding to cardiac troponin C, enhancing myofilament responsiveness to calcium, prolonging the duration of actin-myosin overlap, thereby increasing myocardial contractility but, without increasing intracellular calcium concentration and myocardial oxygen consumption.[3,4] It also has lusitropic actions and exerts peripheral vasodilatory and potential preconditioning effects on myocardium by virtue of its action on mitochondrial adenosine triphosphate-sensitive potassium channels.[5-7] Levosimendan mediates its cardiac inotropic effect via

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the calcium sensitization of the contractile proteins. It has also been suggested that this drug protects the ischemic myocardium and that it decreases the infarct size in coronary-ligated animals.

In the present study, we aimed to compare the efficacy and short-term clinical outcomes of levosimendan versus IABP in patients with low LVEF undergoing OPCABG.

PATIENTS AND METHODS

This prospective, randomized-controlled study was conducted at Lokmanya Tilak Municipal General Hospital and Medical College, Sion, Mumbai between January 2019 and September 2019. The patients who underwent OPCABG with a low LVEF (<25%) were included. Patients undergoing emergency OPCABG or concurrent procedures in addition to OPCABG such as congenital, valve, or aortic surgery, those treated with levosimendan within the past three months or with other inotropes within the previous week were excluded from the study. Patients with significant pulmonary disease, renal dysfunction, liver dysfunction, redo-OPCABG, or arrhythmias with bundle branch block and those who did not survive for 48 h after surgery due to surgery-related causes were also excluded. A written informed consent was obtained from each patient. The study protocol was approved by the Lokmanya Tilak Municipal General Hospital and Medical College Ethics Committee and Institutional Review Board (IEC/38/18). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The LVEF was measured using transthoracic echocardiography (TTE) both preoperatively and postoperatively.

In the given period, we operated 82 patients with low LVEF (<25%), of which 68 patients were eligible for the study, of which only 64 patients consented. Of these, only 60 patients (44 males, 16 females; mean age 60.58+5.23 years; range, 42 to 70 years) survived for 48 h and were included in the study. These 60 patients were divided into two equal groups including 30 in each as follows: levosimendan (Group L) and IABP (Group B). The patients were randomly assigned to the respective groups. Randomization was carried out through the random allocation via computer-generated random numbers.

Management protocol

All patients were admitted to the cardiac intensive care unit (ICU) 24 h prior to surgery. A Swan-Ganz catheter was inserted for pulmonary artery pressure monitoring and radial arterial cannulation was performed for systemic arterial monitoring. The levosimendan or IABP therapy was started 24 h prior to surgery in the respective groups.

In Group L, patients received a preoperative dose of levosimendan (Inj. Semenda-12.5 mg/mL, Lupin lab.) 200 µg/kg dose dissolved in 50 mL of normal saline (NS) and started at a rate of 2 mL/h for 24 h.

In Group B, the IABP was inserted through the femoral artery by the percutaneous technique using an 8F IABP catheter (Arrow International, Reading, PA, USA) connected to the Arrow® pump. The position of the balloon was confirmed by radiography. Heparin infusion was started at a rate of 5 to 10 U/kg/h to maintain the activated coagulation time within 140 to 160 sec.

All patients underwent continuous monitoring of heart rate (HR), ambulatory blood pressure (ABP), cardiac index (CI), mean arterial pressure (MAP), and pulmonary capillary wedge pressure (PCWP). Central venous pressure (CVP), urine output, Vasoactive Inotropic Score (VIS), and lactate levels were also monitored. Hemodynamic parameters recorded at various time points before or after the drug were administered or IABP was inserted. All the parameters were measured at regular time points, i.e., at baseline (T0), 30 min (T1) after beginning levosimendan or IABP, 6 h (T2), 12 h (T3) after starting levosimendan or IABP respectively, prior to induction (T4), 15 min after induction (T5), immediately after completion of revascularization (T6), 6 h after surgery (T7), 12 h after completion of surgery (T8), 24 h after surgery (T9), and 48 h after surgery (T10).

Anesthetic management and surgical procedures were the same in both groups. Induction and maintenance of general anesthesia with endotracheal intubation was standardized in both groups. All procedures were performed using the off-pump technique. The OPCABG was performed using the left internal mammary artery (LIMA) and reversed saphenous vein grafts (rSVGs) as conduits. Left anterior descending (LAD) artery was revascularized by LIMA, while other coronary arterial targets were revascularized by rSVGs via an aortocoronary anastomosis.

Definitions

High inotropic support was defined as the requirement of dobutamine >5 μg/kg/min and/or adrenaline >0.1 μg/kg/min and/or noradrenaline >0.1 μg/kg/min. The VIS was calculated as a weighted sum of all administered inotropes and vasoconstrictors, reflecting pharmacological support of the cardiovascular system.[8] It was calculated using the formula described by Koponen et al.,[9] during the first 48 h after postoperative ICU admission, which were retrieved from the ICU critical care information system.

Low cardiac output syndrome (LCOS) was defined as the presence of low CI (<2.2 L/min/m^2) with elevated PCWP (>16 mmHg) and a partial pressure of arterial oxygen (PaO_2) of <60 mmHg. Acute renal failure was defined when serum (S) creatinine increases by >50% from baseline with or without oliguria (urine output <0.5 mL/kg/h) or requiring dialysis.[8]

Cerebrovascular accidents were defined, if there was development of a new focal neurological deficit or coma persisting for >48 h, after metabolic causes were ruled out.[3] A neurological alteration persisting <48 h was considered as a transient ischemic attack. Postoperative mortality was defined as death occurring during hospitalization or within 30 days after surgery.

Statistical analysis

Statistical analysis was performed using the SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The Student's t-test and analysis of variance (Wilcoxon signed-rank test) were used to determine the differences between the groups. The multiple measures analysis of variance (ANOVA) was used for within the group analysis. A p value of <0.05 was considered statistically significant.

RESULTS

Demographic data, nature of the disease, and surgical characteristics of all patients were comparable in both groups (Table 1). Baseline hemodynamic parameters and serum lactate concentrations were also comparable in both groups. Hemodynamic data were recorded and compared at various time points. Preoperative ICU stay was uneventful in both groups. Seven patients in Group L developed mild hypotension, which resolved with fluid resuscitation. Two patients (n=1 in each group) required vasopressors support and one patient in Group B required removal of IABP due to limb ischemia and re-insertion of IABP in the opposite femoral artery.

Table 1
Baseline demographic and clinical characteristics of patients

	Levosimendan (Group L) (n=30)		IABP (Group B) (n=30)		
Variable	n	Mean±SD	n	Mean±SD	p
Age (year)	30	60.2±5.7	30	161.2±8.5	0.55
Sex					0.55
Male	23		21		
Female	7		9		
Height (m)		162.4±7.3			
Weight (kg)		65.6±6.3		66.6±6.9	0.56
Hypertension (%)	19/30		20/30		0.78
Diabetes mellitus	21/30		22/30		0.77
Left ventricular ejection fraction		20.5±4.4		20.4±4.52	0.93
Number of grafts		2.6+0.8		2.5+0.8	0.64
Baseline serum creatinine (mg/dL)		1.1±0.2		1.2±0.1	0.15
Hemoglobin (%)		13.5+0.8		13.4+0.8	0.62

IABP: Intra-aortic balloon pump; SD: Standard deviation.

Hemodynamic data recorded at baseline were comparable in both groups (Tables 2, 3). A progressive increase in the CI was observed in both groups. The increase was observed to be statistically significant on within the group in both groups. However, the differences in the CI at different time points between

Table 2
Hemodynamic variables at time points

	HR	MAP	VIS
Time	Mean±SD	Mean±SD	Mean±SD
Time 0			
Group L	70.8±7.1	90.2±4.3	1.9±0.4
Group B	71.9±8.3	88.4±6.6	1.7±0.6
P	0.59	0.21	0.17
Time 1			
Group L	78.2±7.1	84.1±6.1	1.8±0.5
Group B	77.9±8.3	86.1±7.2	1.6±0.3
P	0.86	0.24	0.06
Time 2			
Group L	68.8±5.3	86.1±5.3	1.6±0.5
Group B	70.7±6.3	88.3±6.4	1.6±0.9
P	0.22	0.15	1
Time 3			
Group L	74.8±6.1	85.4±6.9	1.8±0.8
Group B	74.7±7.3	88.5±7.2	1.7±0.8
P	0.91	0.1	0.63
Time 4			
Group L	80.2±4.3	88.5±4.1	2.1±0.9
Group B	78.9±6.6	87.4±6.4	2.3±1.1
P	0.32	0.43	0.44
Time 5			
Group L	88.2±7.1	82.2±8.0	5.7±2.1
Group B	90.8±4.3	80.4±7.2	6.4±1.8
P	0.09	0.36	0.17
Time 6			
Group L	84.2±7.1	88.8±5.9	6.3±2.3
Group B	83.9±8.4	88.6±6.6	6.9±2.7
P	0.87	0.9	0.35
Time 7			
Group L	75.2±9.2	88.4±5.9	6.4±2.1
Group B	76.9±8.5	86.5±6.4	7.1±2.6
P	0.46	0.21	0.25
Time 8			
Group L	76.2±8.1	88.4±5.9	5.4±1.8
Group B	75.6±8.3	86.3±6.4	6.1±2.3
P	0.77	0.19	0.19
Time 9			
Group L	68.8±4.3	84.1±6.1	3.7±1.3
Group B	69.2±6.2	86.1±7.2	4.2±1.5
P	0.81	0.24	0.17
Time 10			
Group L	66.5±5.1	88.7±5.9	1.9±0.8
Group B	65.5±6.3	87.5±6.8	1.7±1.1
P	0.5	0.47	0.42

HR: Heart rate; MAP: Mean arterial pressure; VIS: Vasoactive Inotropic Score; SD: Standard deviation.

Table 3
Data at various time points

	PCWP	CI	Lactates
Time	Mean±SD	Mean±SD	Mean±SD
Time 0			
Group L	20.5±2.5	2.1±0.2	1.7±0.4
Group B	19.2±3.0	2.1±0.2	1.8±0.6
P	0.08	0.55	0.68
Time 1			
Group L	15.9±2.5	2.2±0.2	1.7±0.3
Group B	12.7±2.4	2.2±0.2	1.7±0.4
P	<0.0001*	0.57	0.9
Time 2			
Group L	16.34±3.27	2.1±0.3	1.6±0.2
Group B	15.63±1.26	2.2±0.4	1.7±0.6
P	0.27	0.38	0.72
Time 3			
Group L	15.6±3.7	2.3±0.2	1.8±0.1
Group B	15.0±2.8	2.2±0.3	1.6±0.5
P	0.41	0.09	0.08
Time 4			
Group L	15.2±4.3	2.1±0.2	2.0±0.2
Group B	16.7±3.9	2.1±0.2	1.8±0.8
P	0.15	0.24	0.13
Time 5			
Group L	14.3±3.3	2.2±0.2	1.8±0.4
Group B	14.7±2.3	2.2±0.1	1.7±0.5
P	0.67	0.48	0.27
Time 6			
Group L	15.3±3.3	2.2±0.1	1.7±0.3
Group B	14.6±2.3	2.2±0.3	1.6±0.6
P	0.33	0.85	0.56
Time 7			
Group L	16.3±3.2	2.2±0.2	1.6±0.3
Group B	15.7±1.6	2.2±0.2	1.5±0.7
P	0.35	0.84	0.22
Time 8			
Group L	15.6±3.7	2.2±0.1	1.7±0.2
Group B	14.2±1.6	2.2±0.2	1.7±0.5
P	0.18	0.09	0.54
Time 9			
Group L	16.3±3.3	2.2±0.3	1.6±0.4
Group B	15.7±1.6	2.2±0.2	1.5±0.9
P	0.32	0.47	0.35
Time 10			
Group L	16.3±3.2	2.3±0.1	1.6±0.3
Group B	15.6±1.3	2.2±0.2	1.5±0.7
P	0.29	0.12	0.19

PCWP: Pulmonary Capillary Wedge Pressure; CI: Cardiac Index; SD: Standard deviation.

Table 4
Postoperative findings and outcomes

Variable	Levosimendan (Group L)			IABP (Group B)			p
	n	%	Mean±SD	n	%	Mean±SD	
Ventilation time (h)			8.5+4.1			9.7+7.2	0.17
Blood loss in first 24 hrs (mL/kg)			5.7+3.4			5.3+2.7	0.58
Need for inotropic support	7/20	35		6/20	30		0.75
Postoperative atrial fibrillation (%)	4/30	13.33		12/30	40		0.01
LCOS (%)	2/30			2/30			1
Norepinephrine requirement (%)	14/30			15/30			0.79
ICU stay (days)			4.4+0.2			6.5+0.1	<0.001
Hospital stay (days)			10.1+1.0			13.3+0.1	<0.001

IABP: Intra-aortic balloon pump; LCOS: Low cardiac output syndrome; ICU: Intensive care unit; SD: Standard deviation.

the two groups were not statistically significant. The PCWP decreased in both groups; however, the decline was not statistically significant, either. Serum lactate concentration was consistently lower in Group B compared to Group L at all time points. However, this difference was not statistically significant. The HR, MAP, and VIS were comparable in both groups at all time points.

The mean ICU stay in Group B was 6.5+0.1 days compared to Group L (4.4+0.2 days), indicating a statistically significant difference (p<0.001). The patients in Group B had delayed hospital discharge at 13.4 days, compared to Group L (10.2 days), indicating a statistically significant difference (p<0.001).

Two patients in Group B required femoral artery embolectomy due to development of acute thrombosis. None of the patients in Group L and Group B developed acute kidney injury. The incidence of postoperative atrial fibrillation was lower in Group L, compared to Group B, indicating a statistically significant difference (p=0.01). Noradrenaline requirement (%) and incidence of LCOS were similar in both groups. Totally, two patients (one in each group) died due to sepsis and multiple organ dysfunction. The length of ICU and hospital stay were higher in Group B, compared to Group L, indicating a statistically significant difference (p=0.001).

DISCUSSION

Off-pump coronary artery bypass grafting involves displacement and manipulation of heart to expose target coronary arteries, particularly obtuse marginal and posterior descending coronary arteries. This manipulation may be accompanied by transient annular mitral distortion, leading to acute mitral regurgitation, compression of pulmonary veins and/or the right ventricle in addition to superimposed impaired cardiac contractions due to the epicardial stabilizer. This results in hemodynamic instability in the form of increased filling pressures, right ventricular end-diastolic pressure and transient diastolic dysfunction.[10,11] All these changes are exaggerated intraoperatively in patients with LV dysfunction, which is the main risk factor for intra- and postoperative LCOS.[12,13]

The main challenge during OPCABG is to maintain optimum hemodynamics. This can be achieved by mechanical or pharmacological means. Use of inotropes constitutes major pharmacological intervention and its appropriate selection helps in better clinical outcomes. However, conventional inotropes such as beta-agonists and phosphodiesterase inhibitors are associated tachycardia and arrhythmia, leading to an increased myocardial oxygen demand.[14]

Levosimendan is a novel inotropic agent. It also provides beneficial immunomodulatory, cardioprotective, anti-stunning, anti-ischemic, anti-inflammatory, and antioxidant effects to improve cardiac performance in the presence of ischemia.[15-18] All these characteristics make it a near-ideal inotrope in patients with LV dysfunction.

The IABP counter pulsation is currently the most used mechanical assistance device for patients with cardiogenic shock due to acute myocardial

infarction. Its beneficial physiological effects have been established. The IABP increases diastolic blood pressure.[19,20] and, thus, it improves diastolic coronary perfusion. Furthermore, it increases cardiac output and stroke volume by reducing afterload. The ability to act on diastolic pressure has a great importance in clinical practice, since the elevated diastolic pressure results in a redistribution of coronary blood flow toward ischemic areas of the myocardium.[21]

A multi-center study showed that prophylactic use of IABP improved outcomes in high-risk cardiac patients.[22] The main disadvantages of IABP, particularly in patients with systemic atherosclerosis, is the development of complications associated with instillation of the balloon including includes limb ischemia, damage to the vessels, and bleeding.[23,24]

This study highlights the favorable hemodynamic profile of levosimendan and IABP in terms of reduced PCWP and improved CI after its administration. We consistently observed higher CI in patients treated with IABP during intra- and postoperative period, compared to levosimendan; however, the increase was not statistically significant. The rise in CI leads to reduced serum lactate concentrations, indicating improved microcirculation at peripheral tissue level. Although data are scarce regarding the use of levosimendan during cardiac surgery in patients with low EF, our results are consistent with the recent studies.[24] In a meta-analysis, Landoni et al.[21] emphasized that the use of levosimendan contributed to a significant reduction of mortality in cardiac patients with favorable outcomes. In the study conducted by Alvarez et al.,[25] they concluded that a loading dose of levosimendan needed to be omitted in decompensated heart failure patients to prevent hypotensive episodes. Hence, we preferred an approach of gradually achieving the therapeutic concentration without causing any hypotensive episodes in our institution.

In the current study, none of the patients developed significant hypotension, any hemodynamic instability, and other side effects such as nausea and headache in the preoperative period and the regime was tolerated well. Immediate postoperative outcomes also improved in the levosimendan group with a notably reduced incidence of postoperative atrial fibrillation which can be attributed to antioxidant and anti inflammatory properties of levosimendan.[23] Although several studies have emphasized the increased incidence of ventricular arrythmias after administration of levosimendan, we found no similar result in our study.

In their study, Baysal et al.[26] suggested that levosimendan increased renal blood flow by decreasing renal vascular resistance and increasing glomerular filtration rate. In another study using propensity score analysis, Lorusso et al.[27] concluded that patients with IABP support in the preoperative period had a lower risk of acute kidney injury. Our findings are also consistent with the aforementioned studies, as none of our patients developed acute kidney injury requiring dialysis.

Furthermore, we observed a decreased incidence of LCOS in both groups. These findings can be attributed to favorable surgical conditions produced by levosimendan and IABP owing to improved myocardial contractility and reduced pulmonary pressures which make the heart supple and easy to operate upon. In another study, Lomivorotov et al.[28] compared levosimendan and IABP in high-risk cardiac surgery patients and concluded that the infusion of levosimendan after anesthesia induction in cardiac surgical patients contributed to lower cardiac troponin I concentrations and improved hemodynamics compared to preoperative IABP. Similarly, Severi et al.[29] also observed a shorter ICU stay in patients pretreated with levosimendan compared to patients receiving prophylactic IABP. In our study, we found a significant difference in the length of ICU and hospital stay between the two groups. The patients in Group B stayed in the ICU for a longer duration (mean 6.5±0.1 days) compared to the patients in Group L (mean 4.6±0.2 days) group. Although two patients in Group B needed an additional procedure in the form of an embolectomy, it did not influence the total ICU stay in the study population.

The single-center design is the main limitation of the present study. In addition, we were unable to consider serum-specific cardiac markers (troponin levels) which would in detail highlight the cardiac status of the patients in both groups. Also, the immediate postoperative mortalities (within 48 h) were unable to be analyzed.

In conclusion, the use of prophylactic levosimendan is comparable to prophylactic IABP, when hemodynamic parameters are taken into consideration. Prophylactic levosimendan is associated with lower hospital and ICU stay. Prophylactic levosimendan can be considered as an alternative to prophylactic IABP in patients with low ejection fraction in whom IABP is contraindicated.

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Cardiovascular Surgery and Interventions

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Factors associated with medication non-adherence among patients on hemodialysis: A cross-sectional study

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ABSTRACT

Objectives: In this study, we aimed to evaluate the factors associated with medication non-adherence in terms of motivation and knowledge levels among hemodialysis-dependent patients.

Patients and methods: Between March 2018 and April 2018, 134 Caucasian patients (78 males, 56 females; mean age 64.1±13.0 years; range, 23 to 86 years) on hemodialysis at two dialysis centers were included in this cross-sectional study. The Modified Morisky Scale was administered to assess the patients' levels of motivation and knowledge about their medications.

Results: The mean time on hemodialysis was 52.3±50.8 months and the mean number of prescribed medications was 7.5±3.5. The ratio of patients with a low level of motivation and knowledge were 17.2% and 11.9%, respectively. Hypertension was found to be an independent risk factor for low level of motivation (adjusted odds ratio [aOR]: 5.260 [95% confidence interval [CI]: 1.122-24.665], p=0.035). Being employed was found to be an independent risk factor for low level of knowledge (aOR: 5.000 [95% CI: 0.404-6.219], p=0.01).

Conclusion: Hypertension and being employed were found to be associated factors of non-adherence to medication therapy. Healthcare professionals should recognize the factors associated with non-adherence and perform effective interventions to prevent adverse outcomes of non-adherence among patients receiving hemodialysis.

Keywords: Hemodialysis, knowledge, medication non-adherence, motivation.

Hemodialysis (HD) is a life-saving procedure in the treatment of end-stage renal disease, which requires strict adherence. Adherence in HD therapy has four aspects: fluid restriction, dietary restriction, regular use of prescribed medications, and timely participation to HD sessions.[1] Despite the critical importance of adherence, many patients on HD often fail to follow their recommended treatments.[1,2] According to a recent systematic review study, medication non-adherence is highly frequent in patients receiving HD with an average rate of 52.5%.[3]

Most of the patients on HD also experience coexisting chronic diseases requiring long-term medication therapy, resulting in multiple medication use.[4] The average number of medication received by the patients is 10 to 12, while the average number of prescribed medications per day is 19.[3] Moreover, Chiu et al.[5] suggested that patients on HD had the greatest burden of medication among patients with chronic diseases. High burden of medication therapy may lead to non-adherence among patients on HD, and medication non-adherence is related with substantial worsening of medical condition, increased frequency and length of hospitalization, mortality, and increased healthcare costs.[6-8]

Motivation and knowledge of patients about their medications have been commonly accepted as good indicators of adherence behavior, while low levels of motivation and knowledge were known to be associated with non-adherence.[9,10] In this present study, we aimed to investigate sociodemographic and clinical risk factors for low levels of motivation and knowledge, which may be associated with non-adherence to medication therapy.

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PATIENTS AND METHODS

This cross-sectional study was conducted at Istanbul Medeniyet University, Faculty of Medicine, Department of Cardiovascular Surgery between March 2018 and April 2018. The data of 134 Caucasian patients (78 males, 56 females; mean age 64.1±13.0 years; range, 23 to 86 years) receiving HD at two private dialysis centers were collected. Inclusion criteria were as follows: having a sufficient level of talking, hearing, and cognitive ability to complete the questionnaire and being on HD treatment for more than one month. Exclusion criteria were having advanced dementia or having a caretaker for daily care. To limit participants' fatigue, the study visit was scheduled during the first hour of HD. Necessary permissions were obtained from the Directors of the dialysis centers. A written informed consent was obtained from each patient. The study protocol was approved by the Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection

The Modified Morisky Scale (MMS) was used, which is the modified version of 4-item Morisky Medication Adherence Scale (MMAS-4)[11] as suggested by the Case Management Society of America.[9] It is a well-designed and reliable questionnaire which can separately assess levels of motivation and knowledge, affecting non-adherence behavior to medication therapy. It is a six-item questionnaire and all questions are answered on a "Yes" or "No" scale (Table 1). Additionally, the scale is considerably short and practical to perform in vulnerable patient populations as in this study. The data about the characteristics of the patients were obtained from face-to-face interviews and patients' medical records.

Assessment of medication non-adherence

On MMS, Items 1, 2, and 6, which measure forgetfulness and carelessness, were considered to be indicators of motivation. Items 3, 4, and 5, which measure discontinuation of medication and understanding of the long-term benefits of the medication, were considered to be indicators of knowledge.[9] If the answer to each question was "Yes", participants would get 0 point; if "No", participants would get 1 point. Participants who received totally ≤1 point from the Items 1, 2, and 6 were assessed as low-motivated and those with >1 point were assessed as highly motivated. Participants who received totally ≤1 point from the Items 3, 4, and 5 were assessed to have a low level of knowledge and those with >1 point were assessed to have a high level of knowledge.[9]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 24.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The Kolmogorov-Smirnov test was performed to test the normality of the data. Binary logistic regression analysis was conducted to assess the correlations between patient characteristics

Table 1
Modified Morisky Scale

	Question	Motivation	Knowledge
1	Do you ever forget to take your medicine?	Yes (0), No (1)	
2	Are you careless at times about taking your medicine?	Yes (0), No (1)	
3	When you feel better do you sometimes stop taking your medicine?		Yes (0), No (1)
4	Sometimes if you feel worse when you take your medicine, do you stop taking it?		Yes (0), No (1)
5	Do you know the long-term benefit of taking your medicine as told to you by your doctor or pharmacist?		Yes (1), No (0)
6	Sometimes do you forget to refill your prescription medicine on time?	Yes (0), No (1)	
	Total score	- 0-1= Low motivation 2-3= High motivation	- 0-1= Low motivation 2-3= High motivation

Table 2
Sociodemographic and clinical characteristics of patients

Variables	Total (n=134)			Low knowledge (n=16)			High knowledge (n=118)			p	Low motivation (n=23)			High motivation (n=111)			p
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD		n	%	Mean±SD	n	%	Mean±SD	
Age (year)			64.1±13.0			63.9±13.4			64.1±13.0	0.956			59.3±15.0			65.1±12.4	0.060
Sex										0.366							0.100
Female	56	41.8		5	31.3		51	43.2			6	26.1		50	45.0		
Male	78	58.2		11	68.7		67	56.8			17	73.9		61	55.0		
Primary cause of ESRD										0.971							1.000
Diabetic nephropathy	41	30.6		5	31.3		36	30.5			9	39.1		32	29.0		
Hypertensive nephropathy	55	41.0		4	25.0		51	43.2			9	39.1		46	41.4		
Other	28	20.9		5	31.3		23	19.5			4	17.4		24	21.6		
Unknown	10	7.5		2	12.5		8	6.8			1	4.3		9	8.1		
Comorbidities																	
Diabetes mellitus	55	41.0		8	50.0		47	39.9		0.440	13	56.5		42	37.8		0.102
Hypertension	97	72.4		11	68.8		86	72.9		0.729	21	91.3		76	68.5		0.040*
Vascular access type										1.000							0.999
Arteriovenous fistula	115	85.5		16	100.0		99	83.9			20	87.0		95	85.6		
Central venous catheter	18	13.4		0	0.0		18	15.3			3	13.0		15	13.5		
Arteriovenous graft	1	0.8		0	0.0		1	0.8			0	0.0		1	0.9		
Time on HD (month)			52.3±50.8			47.3±28.9			53.0±53.1	0.670			42.5±41.5			54.4±52.3	0.316
Number of medications			7.5±3.5			8.7±4.1			8.5±3.4	0.735			9.2±4.3			8.4±3.3	0.363
Educational status										1.000							1.000
Illiterate	21	15.7		3	18.8		18	15.3			3	13.0		18	16.2		
Literate	5	3.7		2	12.5		3	2.5			1	4.3		4	3.6		
Primary education	78	58.2		9	56.3		69	58.5			15	65.2		63	56.8		
High school	16	11.9		1	6.2		15	12.7			1	4.3		15	13.5		
Bachelor's degree	13	9.7		1	6.2		12	10.2			3	13.0		10	9.0		
Master degree	1	0.8		0	0.0		1	0.8			0	0.0		1	0.9		
Employed	18	13.4		3	18.8		15	12.7		0.011*	7	30.4		11	9.9		0.350
History of smoking	19	14.2		3	18.8		16	13.6		0.578	6	26.1		13	11.7		0.080
Living alone	14	10.4		1	6.2		13	11.0		0.564	1	4.3		13	11.7		0.314
History of kidney transplant	3	2.2		0	0.0		3	2.5		0.999	0	0.0		3	2.7		0.999

ESRD: End-stage renal disease; HD: Hemodialysis; * $p<0.05$.

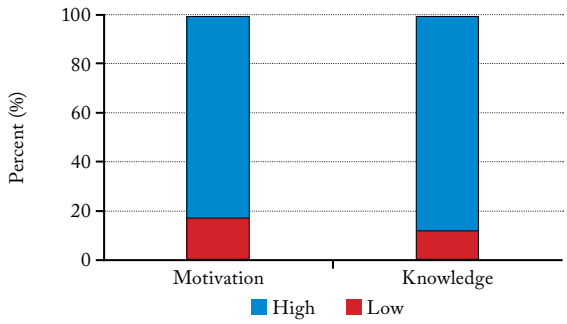

Figure 1. Prevalence of levels of motivation and knowledge of patients.

and levels of motivation and knowledge. On the unadjusted binary logistic regression analyses, the correlations with a significance level below 0.2 were considered confounding factors. To eliminate these factors and to identify the independent risk factors, multiple logistic regression analyses were carried out separately for low level of motivation and low level of knowledge. A two-tailed *p* value of <0.05 was considered statistically significant.

RESULTS

The mean time on HD was 52.3±50.8 (range, 1 to 296) months and the mean number of prescribed medications was 7.5±3.5 (range, 1 to 19). Of the participants, 13.4% were employed and 10.4% were living alone. Regarding comorbidities, 41.0% of patients had diabetes mellitus (DM) and 72.4% had hypertension (HT). All of the patients with HT were on an antihypertensive medication. The patients were on HD via an arteriovenous fistula (85.8%), central venous catheter (13.4%), and arteriovenous graft (0.8%). Baseline sociodemographic and clinical characteristics of the patients are presented in Table 2.

The ratio of low-motivated patients was 17.2%. The ratio of patients who ever forgot to take their medication was 33.6%. A total of 87.3% of the patients were careful about the times of taking their medication, while 18.7% of the patients sometimes forgot to refill their prescribed medications on time. The ratio of patients who had a low level of knowledge was 11.9%. Also, 13.4% of the patients sometimes stopped taking their medication, if they felt better, whereas 14.9% of the patients sometimes stopped taking their medication, if they felt worse. A total of 52.2% patients had no knowledge about the long-term benefits of taking their medication. The prevalence of levels of motivation and knowledge of the patients is demonstrated in Figure 1.

Table 3
Associated factors of medication non-adherence

Variable	OR	95% CI	*p*
Employment status	5.000	0.404-6.218	0.011
Hypertension	5.260	1.122-24.665	0.035

OR: Adjusted odds ratio; CI: Confidence interval.

In unadjusted logistic regression analyses, the patients with HT indicated a low level of motivation (p=0.04), and patients who were employed indicated a low level of knowledge (p=0.01). Although not statistically significant, elderly tended to be highly motivated (p=0.06). Other variables were not found to be associated with the level of motivation or knowledge.

After adjustment for potential confounders, the analysis revealed that patients with HT had a 5.3-fold risk of low level of motivation. The patients who were employed were under 5-fold risk of low level of knowledge. Associated factors of medication non-adherence are listed in Table 3.

DISCUSSION

In the present study, we evaluated the factors associated with medication non-adherence in terms of motivation and knowledge levels among HD-dependent patients. Our study results demonstrated that the ratio of low-motivated patients was 17.2% and the ratio of patients with a low level of knowledge was 11.9%. Hypertension and being employed were found to be associated factors of medication non-adherence in patients receiving HD.

In the literature review, we found only one study comparable with our ratio of patients with a low level of motivation and knowledge. The ratio of the patients with a low level of motivation (17.2%) and knowledge (11.9%) in our study were higher, compared to the study of Ozturk et al.[12] (13.7% and 8.8%, respectively).

A large number of studies have shown that HD patients with comorbidities indicate a low level of adherence.[3,13,14] In our study, we investigated HT and DM, which are the most commonly seen comorbidities

in these patients. Consistent with the results of recent studies, we demonstrated that patients with HT were less motivated, consequently less adherent to medication therapy. Since all of the patients with HT were on antihypertensive medications, it is unclear whether they were less motivated due to HT itself or due to antihypertensive medications. Still, we attribute the non-adherence to medications. A meta-analysis study conducted in Australia investigated non-adherence to antihypertensive drugs in patients on HD and reported that the drugs potentially contributed hypotension after dialysis treatment, and patients may not have any desire to take these medications due to hemodynamic effects they experience.[3,15] Additionally, a comprehensive review study from United States showed that antihypertensive drugs might have unpleasant side effects and provided limited symptomatic relief; therefore, the drugs could adversely affect adherence behavior of patients receiving HD.[8]

Although it did not reach statistical significance, our study demonstrated that younger age might be an independent risk factor for a low level of motivation, consequently for non-adherence to medication therapy. There are many studies in the literature reporting that younger age is a predictor for medication non-adherence.[1,14,16] Possible explanations of this finding include that younger patients may have not accepted that they are affected by a chronic disease and may perceive themselves stronger toward the possible complications of non-adherence. Besides, younger patients may have a more prominent feeling of independence, which can lead to disregard of health problems, and non-adherence behavior.[17] Studies have shown that older patients are more aware of possible complications and have more tendency to be adherent.[1,14]

In the current study, employed patients had a low level of knowledge, consequently low level of adherence to medication therapy, which is similar to the results of previous studies.[1,6,18] Patients who are working may often fail to follow their prescribed medications due to their business and occupational status. They are more involved in daily living activities and may not be willing to pay attention to the requirements of medication therapy, and tend to be more non-adherent.[1]

Studies on the effect of education level on medication non-adherence yield controversial results. Although some studies reported a higher adherence in patients with a higher education level,[4,7] there are studies that have found no association.[1,14] Likewise, we found no statistically significant relationship between education level and medication non-adherence. Of note, patients may not be able to adapt adequately to medications due to some psychosocial reasons, despite their high education level.

A higher number of medication was found to be a significant predictor of medication non-adherence in many studies.[3-5] Due to drug interactions and adverse effects of medications, patients often have difficulty in following their medication therapy.[3,5] Additionally, complexity of medication therapy related to the frequency and dosage schedules is significantly associated with non-adherence.[3] Nonetheless, we found no statistically significant correlation between the number of medication and medication non-adherence which is probably due to having a relatively small sample in the present study.

The results of this study have a number of implications for clinical practice. Healthcare professionals should be aware of factors associated with medication non-adherence in this special patient group, and appropriate adherence improvement plans should be implemented to increase the effectiveness of the treatment.

The Case Management Society of America has suggested adherence guidelines to enhance adherence to medication therapy among patients on HD and explained motivation and knowledge improvement tools in details separately. Long-term benefits of medication therapy and potential consequences of non-adherence should be explained to patients with a low level of knowledge and to their families/personal caregivers via regular educational programs.[9] Patients with a low level of motivation should be managed with motivational interviewing, social support plan, patient reminder systems, and family motivational assessment.[9] Additional adherence improvement methods may reduce complexity of medication therapy, maintenance of relationship between patients and healthcare providers, and early diagnosis of cognitive impairment.[19] Many studies have suggested various adherence improvement recommendations for these patients. However, being aware of factors associated with non-adherence and determining patients' levels of motivation and knowledge should be the initial step in managing non-adherence.

Nonetheless, there are some limitations to this study. First, medication non-adherence was not directly assessed within the frame of this study.

The scale used in this study demonstrated the risk factors of low level of motivation and knowledge of the patients about their medications, and low level of motivation and knowledge were associated with medication non-adherence among patients. Second, we have a relatively small study group. The other limitation is that we investigated only HT and DM, which are two major comorbidities among patients on HD. Despite the limitations, this study has a significant contribution to the literature by highlighting motivation and knowledge perspectives of medication non-adherence among patients on HD. Other scales evaluating medication non-adherence other than MMS were not originally designed to assess the underlying causes of non-adherence behavior. However, approaching the non-adherence problem in the perspectives of motivation and knowledge is essential to establish appropriate adherence improvement plans that correspond to the patients' specific needs. Still, a limited number of studies has been published considering these perspectives of medication non-adherence. Our study, thus, promotes researchers to focus on patients' motivation and knowledge levels.

In conclusion, HT and being employed were found to be independent risk factors for a low level of motivation and a low level of knowledge, respectively. Based on these results, HT and being employed seem to be associated factors of medication non-adherence in patients receiving HD. However, future studies should be conducted for further understanding of factors associated with medication non-adherence among patients on HD. Approaching the non-adherence problem in the perspectives of motivation and knowledge is essential to design appropriate adherence improvement plans.

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Cardiovascular Surgery and Interventions

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The effectiveness of internal compression therapy in deep venous insufficiency

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ABSTRACT

Objectives: The aim of this study was to evaluate the effectiveness of internal compression therapy (ICT) in patients with primary deep venous insufficiency (DVI).

Patients and methods: A total of 13 extremities of 11 patients (4 males, 7 females; mean age 54.3±13.7 years; range, 34 to 76 years) who were diagnosed with primary lower extremity deep venous reflux and underwent ICT for symptomatic DVI between January 2018 and December 2018 were included in this retrospective study. The Venous Clinical Severity Score (VCSS) was performed in all patients in the pre- and postoperative period to assess symptomatic improvements. Control examinations of the patients were performed on post-procedural Day 3 and at 1, 6, and 12 months.

Results: The mean diameter of deep veins was 13.0±1.8 (range, 10.2 to 16.1) mm and the mean distance between the valves was 3.9±1.2 (range, 2.1 to 6.1) mm in the pre-procedural period. The mean reflux time was 3.3±0.5 (range, 2.5 to 4) min. The mean diameter of deep veins was 8.9±1.2 (range, 7.5 to 11.0) mm at 12 months after the procedure. The success of the treatment was 100% after the treatment and on the post-procedural Day 3. The mean VCSS of the patients was 8.1±3.1 (range, 6.0 to 16.0) in the pre-procedural period and 1.1±1.4 (range, 0.0 to 4.0) at 12 months during follow-up (p=0.001).

Conclusion: The ICT appears to be a promising procedure, as it is a minimally invasive, rapid, and effective method for the treatment of patients with DVI.

Keywords: Femoral vein, internal compression therapy, venous insufficiency, venous valves, therapeutics.

Deep venous insufficiency (DVI) is a major public health problem and its incidence increases with aging, female sex, previous deep venous thrombosis (DVT) history, pregnancy, obesity, and smoking.[1] It can occur due to primary valvular insufficiency, congenital valve malformations, or valve malfunction secondary to DVT.[2] Deep venous insufficiency leads to the loss of labor force and health costs by causing infection, extreme swelling, soft tissue ulceration, and DVT.[3] The treatment of DVI is important in decreasing complaints such as pain, swelling, skin pigmentation, and venous ulcer.[4,5] Compression therapy, despite significant improvements of other methods, still remains the cornerstone of conservative treatment.[1] Surgical treatments including venous valvular repair, transposition of vein, neovalve construction, and external valve banding require local or general anesthesia.[4,5] The success of valve reconstruction surgery in the treatment of primary DVI is about 65 to 70% during five-year follow-up.[6,7] Due to their less successful results and impracticality, such surgery procedures are not performed as routine procedures in many centers.[4,6-9]

Internal compression therapy (ICT) with a paravalvular leak device (Invamed, Ankara, Turkey) is a new treatment method for primary DVI (Figure 1). The paravalvular leak device is a device which provides to be delivered a mixture of hyaluronic acid and n-butyl-2-cyanoacrilate (NBCA) hard gel on the outer surface of the vein in the insufficient valve level between the deep vein and muscle fascia. The mixture of hyaluronic acid and NBCA adheres around the valves and forms a granulomatous structure. Thus, this device helps to the valves approach each other and

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boost their functioning.[10] In the current literature, there exist very few studies about the results of this treatment method, as it is a fairly new method. In the present study, therefore, we aimed to evaluate the effectiveness of ICT in patients with primary DVI therapy and to present our one-year follow-up results.

PATIENTS AND METHODS

This retrospective study was conducted at Cardiovascular Surgery Clinics of Kafkas University, Faculty of Medicine Hospital between January 2018 and December 2018. A total of 13 extremities of 11 patients (4 males, 7 females; mean age 54.3±13.7 years; range, 34 to 76 years) who were diagnosed with primary lower extremity deep venous reflux and underwent ICT treatment for symptomatic DVI were included. Inclusion criteria were as follows: ≥18 years of age, primary DVI and having complete follow-up data available at six months and one year postoperatively. Exclusion criteria were as follows: severe ambulation limitation, known thrombophilia syndrome, post-thrombotic etiology, a body mass index of >35 kg/m^2, a deep venous reflux of <2 sec, and severe comorbidity. A written informed consent was obtained from each patient. The study protocol was approved by the Kafkas University, Faculty of Medicine Ethics Committee (Date: 13/05/2020/80576354-050-99/161). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All physical examinations were performed by a cardiovascular surgeon in an outpatient clinic and color Doppler ultrasound (CDUS) scanning was performed by two specialist radiologists. Control examinations of the patients were performed on the post-procedural Day 3 and at 1, 6, and 12 months. In the CDUS examination, the patients were examined in terms of reflux time, grade of deep, superficial, and perforating venous insufficiency, and DVT. In addition, the diameter of the common femoral vein where ICT was applied and the distance between the valves were measured and recorded for each patient during the Valsalva maneuver, while the valves were fully open in the expiratory phase. Pathological venous reflux was defined as venous incompetence (reflux) during CDUS examination set at retrograde flow longer than 0.5 sec in the superficial venous system, the deep femoral vein, and the calf veins, longer than 1 sec in the common femoral, femoral vein.[1] All patients were evaluated according to the Comprehensive Classification System for Chronic Venous Disorders (CEAP) classification and Venous Clinical Severity Score (VCSS) classification. Treatment success was defined as reflux-free deep vein valves. A reflux over 0.5 sec was considered as a failure.

Procedural technique

All ICT procedures were performed under local anesthesia in sterile conditions. The purpose of this procedure is to reduce the diameter of the vein, that is insufficient, and so to reduce the distance between the valves.[10] Therefore, the insufficient valves were found using CDUS (Figure 2). Then, the distance between the insufficient valves and the diameter of the vein were measured at the beginning of the operation. The ICT procedure was performed as previously explained by Yavuz et al.[10] (Figure 3). The first control examination of the patients was performed with CDUS on the post-procedural Day 3 (Figure 4).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD) or median (min-max), while categorical variables were expressed in number and percentage. The Wilcoxon signed-rank test was performed to analyze changes in the VCSS between baseline and follow-up. A p value of <0.05 was considered statistically significant.

RESULTS

Baseline demographic and clinical characteristics of the patients are summarized in Table 1. None of

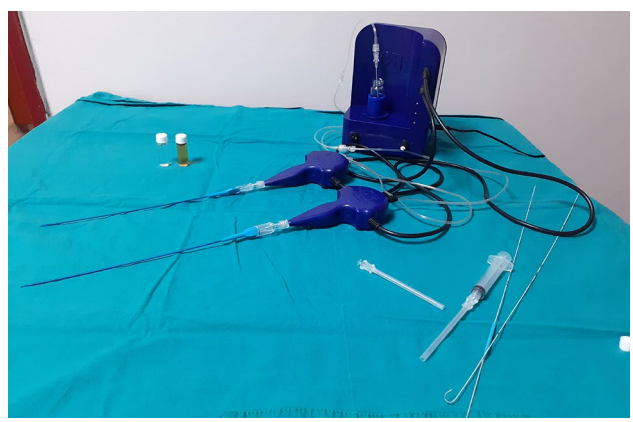

Figure 1. Internal compression therapy Paravalvular Leak Closure Device and Delivery System.

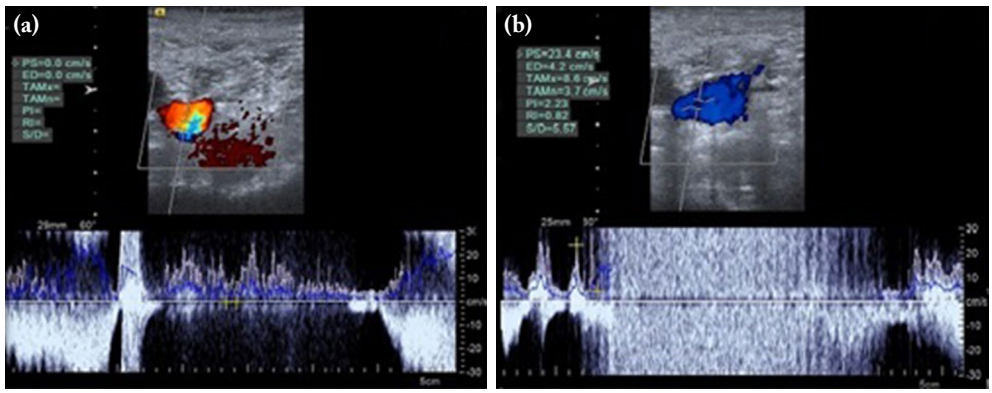

Figure 2. **(a)** A pre-procedural period image of spontaneous venous flow in right main femoral vein during breathing. **(b)** A pre-procedural period image of retrograde reflux flow in right common femoral vein with Valsalva maneuver due to deep venous insufficiency.

the patients had a chronic disease such as chronic renal failure, chronic liver failure, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, or DVT. The CEAP classification in the pre-procedural period was C3 in six lower limbs (46.2%), C4 in six lower limbs (46.2%), and C6 in one (7.7%) lower limb. The mean distance between the valves was 3.9±1.2 (range, 2.1 to 6.1) mm in the pre-procedural period. The mean reflux time was 3.3±0.5 (range, 2.5 to 4) min. The mean procedural time was 22.2±6.4 (range, 15 to 35) min. The mean delivered amount of ICT hard gel was 3.2±0.7 (range, 1.9 to 4.0) mL.

The success of the treatment was 100% immediately after the treatment and on the post-procedural Day 3 with no reflux observed by CDUS in the deep femoral veins. At the six-month follow-up, the results were similar to the post-procedural Day 3 with vein diameters and reflux-free deep veins. At 12 months of follow-up, no significant reflux was observed over 0.5 sec in deep venous vessels on which ICT was applied.

In three of four patients (Patients 2, 3, and 5) who had insufficiency in the proximal vena saphena magna (VSM) in the pre-procedural period, the deficiency in the proximal VSM completely improved in the post-procedural period. Grade 4 insufficiency in the proximal VSM in one patient (Patient 4) improved to Grade 1-2 in the post-procedural period. Since the proximal VSM diameter of the Patients 3 and 4 expanded to 6.0 and 6.9 mm, respectively, while the ICT tight gel was delivered around the insufficient valves in the common femoral vein simultaneously, it was delivered around the saphenofemoral junction (SFJ). However, in two patients (Patients 6 and 9), there was insufficiency in the VSM, not only proximally, but also throughout the VSM. In Patient 6, the diameter of the saphenous vein was 4 mm and, in Patient 9, the diameter of the saphenous vein in the left lower extremity was 8.6 mm at its widest point. In Patient 6, DVI improved in the post-procedural

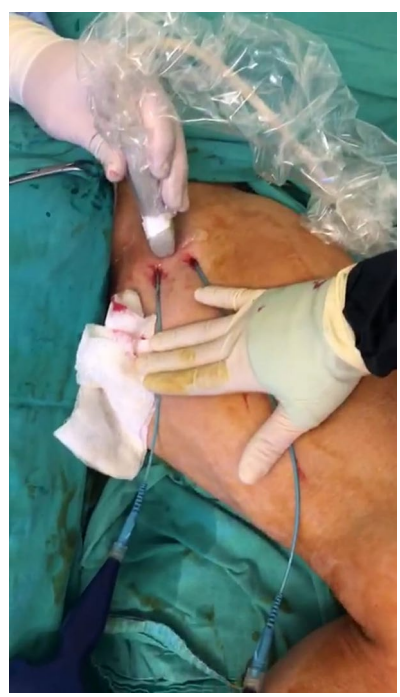

Figure 3. Delivery system cannula placement over to two sides of vein valve.

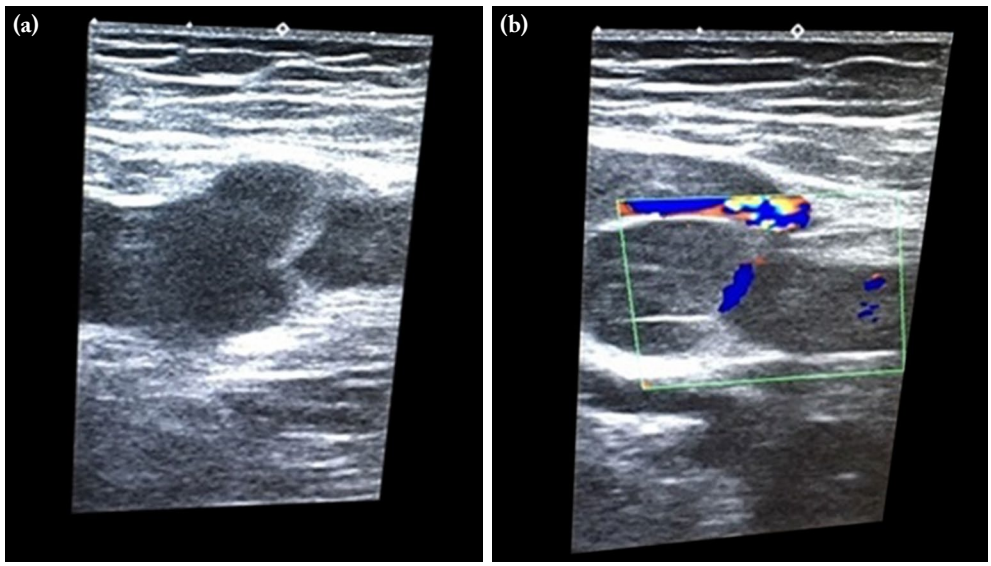

Figure 4. **(a)** A color Doppler ultrasound image of coaptation of early post-procedural period right main femoral vein valve after internal compression therapy. **(b)** An image of minimal deep venous insufficiency of right common femoral vein in early post-procedural period during Valsalva maneuver.

period, although the insufficiency in the VSM did not improve due to a long-segment sickness. The use of compression stockings and medical treatment continued regularly in the post-procedural period in this patient whose edema partially improved with the improvement in DVI. Thus, active ulcer regressed at the post-procedural three months of follow-up. In Patient 9, intravenous cyanoacrylate was performed for saphenous vein failure one month before ICT was performed in the left lower extremity.

Table 1
Baseline demographic and clinical characteristics of patients

Patient/side	Age/Sex	Deep vein diameter (mm)	Distance between valves (mm)	Proximal saphenous vein insufficient reflux (sec)	Deep venous reflux (sec)	CEAP classification	Pre-procedural VCSS
1 right	76/M	12.4	2.1	-	2-3	4	7
1 left		11.9	2.3	-	2-3	4	7
2	34/F	15.2	5.7	2-3	4	3	6
3	59/F	13.9	4.5	2-3	3-4	3	6
4	63/M	12.2	3.9	4	3	4	7
5	34/F	11.5	3.5	2	3	3	6
6	64/M	16.1	6.1	4	3	6	16
7	60/M	13.2	4.1	-	3-4	4	13
8	43/F	13.9	4.3	-	4	4	10
9 right	56/F	12.8	3.7	-	3-4	3	6
9 left		10.2	2.8	4	3-4	3	6
10	43/F	10.5	2.9	-	3	4	7
11	65/F	15.2	5.2	-	4	3	8

CEAP: Comprehensive Classification System for Chronic Venous Disorders; VCSS: Venous Clinical Severity Score.

Table 2
The VCSS scores of patients

Patient/side	VCSS scores			
	Pre-procedural	First month	Sixth month	Twelve month
1 right	7	2	2	1
1 left	7	2	2	1
2	6	0	0	0
3	6	1	1	1
4	7	1	1	1
5	6	0	0	0
6	16	9	4	4
7	13	8	4	4
8	10	2	2	1
9 right	6	0	0	0
9 left	6	0	0	0
10	7	1	1	0
11	8	0	0	0

VCSS: Venous Clinical Severity Score.

Patient 7 had Cockett insufficiency in both pre- and post-procedural period.

There were no mortality and morbidity related to the procedure. No ecchymosis, skin pigmentation, hematoma, paresthesia, deep venous thromboembolism, or pulmonary embolism were observed. The mean VCSS of the patients was 8.1±3.1 (range, 6.0 to 16.0) in the pre-procedural period and 1.1±1.4 (range, 0.0 to 4.0) at 12 months of follow-up (p=0.001). The pre- and post-procedural VCSS are given in Table 2. The mean diameter of deep veins was 13.0±1.8 (range, 10.2 to 16.1) mm in the pre-procedural period and 8.9±1.2 (range, 7.5 to 11.0) mm at the post-procedural 12 months.

DISCUSSION

In this study, we examined the efficacy of ICT in the treatment of lower limbs for primary DVI. Our results showed that the DVI and VCSS of the patients significantly improved at 12 months of follow-up. No morbidity and mortality were observed in any patients.

Although the application of this procedure has been increasing recently, the number of studies reported in the literature is still very small. In a study performed by Yavuz et al.,[10] 43 patients were treated and the mean VCSS score improved from 20.7±5.9 to 3.9±0.9 at 12 months of follow-up. The mean deep vein vessel diameter at the level of the valve was 12.4±2.6 mm in the pre-procedural period, it improved to 9.0±1.7 mm after the procedure. Consistent with this study, the patients included in our study were successfully treated for DVI.

The ICT has certain advantages relative to treatment of DVI with conventional surgical approaches, such as valve reconstruction. After the conventional surgical methods, there is a risk of DVT due to venotomy and the need for anticoagulant treatment to avoid this and, also, the risk of surgical infection and the need for antibiotic prophylaxis to avoid this, in addition to cosmetic concerns.[5,7] Postoperative bleeding, hematoma, and longer hospital stay are the other disadvantages of valve reconstructions. In one study, the mean duration of hospitalization in the postoperative period was five days in conventional reconstructive surgery.[5] However, patients in whom ICT is performed can be often discharged on the same day. In our study, no postoperative adverse conditions were observed, and all patients were discharged on the same day after the procedure. No antibiotherapy or anticoagulant therapy was recommended to the patients.

Currently, valve reconstruction surgery for DVI is mainly performed to provide regression of ulcers

in CEAP Class 5-6 patients.[9] Considering the success and complications of conventional surgery, it is understandable why it is not routinely performed in every center. Also, ICT can be applied to patients with CEAP Class 3-4.[10] Before complications occur, such as perimalleolar ulcer, it can be performed to ensure symptomatic clinical improvement. In our study, the CEAP classification of our patient population was mostly Class 3 and 4, only one patient had perimalleolar ulcer secondary to venous insufficiency. At three months of follow-up, the ulcer healed. In addition, a considerable improvement was observed in the VCSS at 12 months compared to the pre-procedural period. At 12 months of follow-up, as the insufficiency continued along the VSM in Patient 6 and Cockett vein insufficiency persisted in Patient 7, VCSS of these patients improved up to 4.

In the current guidelines, symptomatic venous insufficiency is primarily recommended to be treated for superficial and perforating vein insufficiency. If advanced venous insufficiency (CEAP Class ≥4b) continues despite interventional therapies and compression treatments for superficial venous insufficiency, valve incompetency reconstruction surgery is planned for DVI.[4,9,11,12] However, in the prospective, randomized study of Wang et al.,[8] valvuloplasty for DVI and superficial venous insufficiency treatment were more beneficial than only superficial venous insufficiency treatment in terms of the healing of venous insufficiency and related ulcers. Hardy et al.[13] and Tripathi et al.[14] also suggested that valve reconstructions should be performed for DVI together with superficial vein surgery. In our study, although the symptoms regressed with ICT alone in Patient 6, complete treatment was not provided. In Patient 9, intravenous cyanoacrylate was first applied to the saphenous vein for venous insufficiency in the second leg. However, since DVI did not improve after the procedure, ICT was applied to this leg as well, and the symptoms then improved. Similarly, in the study of Makarova et al.,[15] reflux in the femoral vein did not improve with superficial vein surgery. Considering all these findings, our study results indicate that ICT can be performed as a priority, as the procedure is minimally invasive under local anesthesia and independent from superficial and perforating venous insufficiency surgery. As a matter of fact, in our study, Patients 2 and 5 had proximal VSM insufficiency and we treated them with only ICT. Their complaints improved in the post-procedureal period, although proximal VSM insufficiency was not interfered. As in the work of Eberhardt and Raffetto,[2] we suggest that ICT can be considered primarily in patients with proximal superficial venous insufficiency and DVI, considering that some of the superficial insufficiency may result from DVI. In addition, since the proximal VSM diameter enlarged to 6.0 and 6.9 mm, respectively in Patients 3 and 4 with proximal VSM insufficiency in the pre-procedural period, the leakage was reduced by decreasing the diameter of the VSM in this area by simultaneously delivering the ICT hard gel around the SFJ. Although ICT was performed around the common femoral vein in all patients included in our study, the ICT technique was observed to be a new and improved technique according to the results of these last two patients. We consider that CDUS-guided intervention in the treatment of primary DVI can be performed not only in the region where the common femoral vein-SFJ joins, but also in different segments where the structure and function of the venous valves of the lower extremity are normal. It can be considered that superficial venous insufficiency as well as DVI can be treated with ICT application from multiple levels of subcutaneous tissue into the CDUS-guided paravalvular area. Undoubtedly, we believe that it would contribute to the extension of ICT application indication in selected cases without advanced tortuosity, thrombophlebitis history, post-phlebitic syndrome, or venous packaging.

Nonetheless, there may be certain difficulties in implementing ICT. This therapy can be performed by vascular surgeons with a very good CDUS dominance. The common femoral artery, vein, and nerves are very close to each other anatomically in this region, as well as bifurcation of the deep femoral artery and vein bifurcation in this area are anatomical conditions which increase the difficulty of the procedure. Both axial section and long axis images of deep venous structures and paravalvular area should be well evaluated with CDUS before and during the procedure to avoid complications and to achieve successful results. Otherwise, complications such as potential hematoma, vascular injury, venous valve injury, arterial pseudoaneurysm development, iatrogenic arteriovenous fistula formation, and femoral nerve injury may be inevitable. In addition, if the ICT hard gel is delivered intravenously by mistake, deep venous adhesion and obstruction, and pulmonary embolism can occur. On the other hand, allergic reactions may rarely occur in patients against cyanoacrylate.[16,17]

No evidence of these complications was observed in our patient population. Toxicological, carcinogenic, and mutagenic effects against hyaluronic acid and NBCA have not been observed in vascular use until today.[13,18,19]

The present study has some limitations. The major limitation is its retrospective design with a limited sample size. The retrospective nature of the study precludes the elimination of all potential confounders and biases. Its single-center design conducted by a single specialist for selected patients is another limitation. Nevertheless, in the current literature, there is only one study about the results of this treatment method, as it is a fairly new method. Therefore, we believe that the results of our study would contribute additional information to body of knowledge in the current literature.

In conclusion, internal compression therapy procedure appears to be promising, since it is minimally invasive, rapid, and effective method for the treatment of patients with deep venous insufficiency as an alternative treatment modality of conventional valve reconstruction surgery. In addition, this procedure can be applied under outpatient conditions due to the ease of application, postoperative early recovery, and satisfactory cosmetic results. For internal compression therapy applications in deep and superficial venous insufficiency, further large-scale, prospective, randomized studies are needed.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Cardiovascular Surgery and Interventions

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Transarterial computed tomography angiography before and after endovascular aortic repair in patients with chronic kidney disease

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ABSTRACT

Objectives: In this study, we aimed to evaluate the accuracy of transarterial computed tomography angiography (TA-CTA) in treatment planning and follow-up and to identify the contrast-induced nephropathy (CIN) risk of this procedure in patients with chronic kidney disease (CKD).

Patients and methods: Between November 2012 and November 2013, a total of 14 patients (13 males, 1 female; mean age 73.8±7.2 years; range, 58 to 90 years) with CKD and an aortic aneurysm who underwent TA-CTA were included in this study. A flush catheter was placed in the aorta and CTA images were obtained by 64-slice multidetector computed tomography (MDCT). For the thoracoabdominal TA-CTA, a mixture of 16 mL contrast + 84 mL saline was used, while for the abdominal TA-CTA, 8 mL of contrast + 42 mL of saline mixture was used. These mixtures were injected with an automatic injector without delay in time. The image quality scores (IQS) were between 1 and 4. Serum creatinine and estimated glomerular filtration rate (eGFR) values were obtained before the procedure, and on Days 2-5 and at Months 1-3 after the procedure.

Results: None of the patients developed CIN. The mean creatinine levels were as follows: 2.35 mg/dL before the procedure, 2.27 mg/dL on Days 2-5, and 2.28 mg/dL at Months 1-3 (p=0.084 and 0.109, respectively). The mean eGFR values were as follows: 32.2 mL/min/1.73 m^2 before the procedure, 34.2 mL/min/1.73 m^2 on Days 2-5, and 34.6 mL/min/1.73 m^2 at Months 1-3 (p=0.061 and 0.017, respectively). The Hounsfield unit (HU) values were as follows: 184 to 251 HU (mean: 230 HU) on the distal ascending aorta, 104 to 430 HU (mean: 198 HU) on the renal artery level of the abdominal aorta, 104 to 430 HU (mean: 198 HU) at the terminal aorta, 88 to 406 HU (mean: 183 HU) on the common iliac arteries, and 103 to 274 HU (mean: 171 HU) on the common femoral arteries The HU value was measured in a non-enhanced area as 22 to 45 HU (mean: 32 HU). The mean IQS of Observer 1 and Observer 2 was 3.52 and 3.47, respectively. Only one TA-CTA procedure was scored differently. The mean IQS was 3.495 with an intra-observer agreement of 94%.

Conclusion: Despite its invasive nature, diluted, low-contrast enhanced TA-CTA is an easy-to-use and safe method which provides sufficient anatomical details without causing any nephropathy risk.

Keywords: Chronic kidney disease, computed tomography angiography, contrast-induced nephropathy, contrast material, endovascular aortic repair.

Computed tomography angiography (CTA) is a standard imaging method used in endovascular aortic aneurysm repair (EVAR) planning and follow-up.[1,2] The side effects on kidney functions of the non-ionic contrast material used in this procedure are well known. Among the risk factors of contrast-induced nephropathy (CIN), there are increased creatinine levels, dehydration, congestive heart failure, particularly for individuals over the age of 60, and using nephrotoxic drugs.[3,4] Aortic aneurysm is frequently observed in elderly and is often accompanied by renal dysfunction and diabetes.[5] Therefore, non-ionic contrast materials should be used more carefully in this group of patients.

Frequent abdominal CTA may be needed before and after EVAR. Also, during the endovascular treatment, a high amount of contrast material can be used. Subsequent use of contrast agent may particularly increase the risk of contrast nephropathy in patients with renal insufficiency.

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In the present study, we, for the first time, aimed to evaluate the effectiveness of TA-CTA in treatment planning and follow-up with low-dose non-ionic contrast agent and to identify the CIN risk of this procedure in patients with chronic kidney disease (CKD).

PATIENTS AND METHODS

Between November 2012 and November 2013, a total of 14 patients (13 males, 1 female; mean age 73.8±7.2 years; range, 58 to 90 years) with CKD and an aortic aneurysm who were admitted to the interventional radiology clinic of Ankara Atatürk Training and Research Hospital and underwent TA-CTA were included in this study. Kidney function tests before and after the procedure were performed, and the effectiveness of the procedures before and after EVAR were prospectively evaluated. Newly diagnosed or patients with EVAR due to aortic aneurysm with a baseline serum creatinine level of >1.2 mg/dL and baseline estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 with Grade ≥3 renal insufficiency were included in the study. None of the patients had a history of contrast-related allergies or asthma. None of the patients underwent imaging studies of the aorta within the last three months before TA-CTA which was performed for EVAR planning of. A written informed consent was obtained from each patient. The study protocol was approved by the Ankara Atatürk Training and Research Hospital Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Operative technique

Before the TA-CTA procedure, a 5F sheath was placed in the brachial or femoral artery of all patients. Afterwards, a 5F flush catheter (Boston Scientific, Global Park, Heredia, Costa Rica) was placed into the proximal descending thoracic aorta of the patients with a thoracoabdominal aortic aneurysm (TAAA), and into the 8 to 10 thoracic vertebrae level in the patients with an abdominal aortic aneurysm (AAA). The patients were taken to the CT unit immediately after 2,500 IU of heparin anticoagulation was injected through the flush catheter. The CT scans were obtained with a 64-slice multidetector computed tomography (MDCT) (Aquillion, Toshiba Medical System, Nasu, Japan) device with 0.5-mm slice thickness. For AAAs, 8 mL contrast agent + 42 mL normal saline mixture was injected, while for TAAAs, 16 mL contrast agent + 84 mL saline mixture was injected through the flush catheter. Iso-osmolar iohexol, a third-generation contrast agent, was used. The diluted contrast was injected with an automatic injector, through the flush catheter at a speed of 7 mL/sec with a pressure of 600 mmHg (Medrad Avanta, Pittsburgh, PA, USA). The MDCT scanning was started with the contrast injection simultaneously, and no delay time was used.

Two radiologists with four and 12 years of experience evaluated the CT scans separately. The Hounsfield unit (HU) values were measured at the non-enhanced proximal aortic region, distal thoracic aorta, at the renal artery level of the abdominal aorta, terminal aorta, common iliac arteries, and common femoral arteries. The image quality scores (IQS) was graded from 1 to 4, such that the TA-CTA parameters to be met (Table 1). Then, the intra-observer agreement was evaluated regarding the given IQS. The IQS of TA-CTA of 8 mL and of 16 mL contrast agent were compared separately. The patients who underwent TA-CTA after EVAR were evaluated with color Doppler ultrasound (CDUS) (Logic E9; GE, Milwaukee, Wl, USA) for endoleak by a third

TABLE 1
TA-CTA parameters of image quality scores

Image quality score	TA-CTA parameters
1. Poor	Only proximal segments of visceral arteries and iliac arteries are seen as well as aorta on the axial images
2. Adequate	Distal branches of visceral arteries and femoral arteries are seen as well as aorta on the axial images
3. Good	Only proximal segments of visceral arteries and iliac arteries are seen as well as aorta on the axial and volume rendered images
4. Excellent	Distal branches of visceral arteries and femoral arteries are seen as well as aorta on the axial and volume rendered images

TA-CTA: Transarterial computed tomography angiography.

experienced radiologist. Any difference between the TA-CTA and CDUS in terms of endoleak detection was evaluated.

In addition to the renal insufficiency risk, the patients were evaluated for additional risk factors such as old age, diabetes, use of nephrotoxic drugs, and hypertension regarding CIN. Possible nephrotoxic drugs were discontinued in all patients 24 h prior to the procedure. At least three days before the procedure, the patients were put on minimum 3 liters of oral fluid intake. After the procedure, 1 to 1.5 mL/kg/h of intravenous hydration was administered for 6 h. All patients received 600 mg of oral n-acetylcysteine twice daily for one week, starting two days before the procedure. The highest serum creatinine levels on Days 2-5 and at Months 1-3 after the procedure, and the lowest eGFR values at the same period of time were recorded. These laboratory values were evaluated regarding CIN. Changes in kidney function tests were compared in patients receiving 8 mL and 16 mL of contrast agent.

Statistical analysis

Statistical analysis was performed using the SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The Wilcoxon signed-rank test was used to compare significant differences between baseline creatinine and eGFR values on Days 2-5 and at Months 1-3. The Mann-Whitney U test was used for the comparison of the changes in kidney function tests and the differences in TA-CTA IQS in the patients receiving 8 mL and 16 mL of contrast agent. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 14 patients, four thoracoabdominal TA-CTA procedures were performed in three patients with TAAAs, and 13 abdominal TA-CTA procedures were performed in 11 patients with AAAs. In total, 17 TA-CTA procedures were performed. Brachial artery catheterization was performed in seven procedures, and femoral artery catheterization was performed in 10 procedures. A pigtail catheter as a flush catheter was used in all 17 procedures. None of the patients developed complications such as hematoma or pseudoaneurysm.

Besides renal insufficiency, all patients had hypertension, eight had diabetes mellitus, and two had congestive heart failure. Twelve of the patients were above 60 years of age. Also, five of the patients using angiotensin-converting enzyme inhibitors were

TABLE 2
Baseline demographic and clinic characteristics of patients

No	Age/Sex	Diabetes mellitus	Hypertension	Congestive heart failure	Hospitalization day	Intensive care unit	Post intervention complication
1	69/M	Yes	No	No	1	No	No
2	74/F	Yes	No	No	1	No	No
3	90/M	Yes	Yes	No	1	No	No
4	77/M	Yes	Yes	No	1	No	No
5	58/M	Yes	Yes	Yes	1	No	No
6	71/M	Yes	No	No	1	No	No
7	67/M	Yes	Yes	Yes	1	No	No
8	81/M	Yes	No	No	1	No	No
9	59/M	Yes	Yes	No	1	No	No
10	72/M	Yes	Yes	No	1	No	No
11	78/M	Yes	Yes	No	1	No	No
12	80/M	Yes	No	No	1	No	No
13	75/M	Yes	No	No	1	No	No
14	82/M	Yes	Yes	No	1	No	No

Number 5, Number 6, and Number 9 had two interventions at different times before and after endovascular aortic aneurysm repair.

TABLE 3
Hounsfield unit values measured from different anatomical sites with TA-CTA

Unenhanced aortic area		Distal descending thoracic aorta		Abdominal aorta at renal artery level		Terminal aorta		Common iliac artery		Common femoral artery	
HU	Range	HU	Range	HU	Range	HU	Range	HU	Range	HU	Range
32	22-45	230	184-251	207	104-410	198	104-430	183	88-406	171	103-274

HU: Hounsfield unit; TA-CTA: Transarterial computed tomography angiography.

prescribed a different class of antihypertensive drugs by the treating nephrologist. In three patients using metformin, the drug was discontinued 48 h prior to the procedure to prevent the peril of lactic acidosis. After the procedure, serum creatinine levels were measured, and the drug was re-initiated. Baseline demographic and clinical characteristics of the patients are presented in Table 2.

The mean HUs of the aorta measured during the TA-CTA procedures on different anatomical localizations are shown in Table 3. All TA-CTA procedures were separately evaluated by two observers according to the IQS TA-CTA criteria. None of the procedures received 1 (negative) IQS score. Observer 1 graded 11 procedures with IQS 4, four procedures with IQS 3, and two procedures with IQS 2. Observer 2 graded 10 procedures with IQS 4, five procedures with IQS 3, and two procedures with

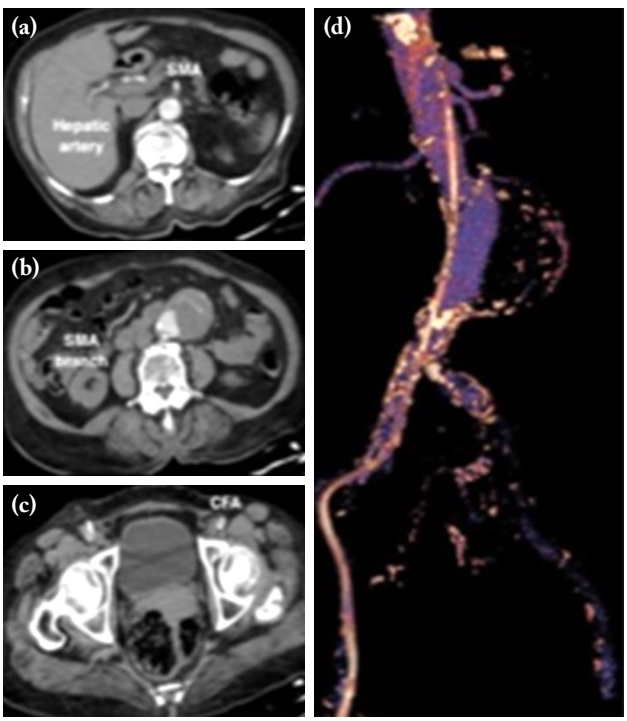

Figure 1. An example for IQS 2. TA-CTA images performed on an 86-year-old woman with an abdominal aortic aneurysm and chronic kidney disease before EVAR. On axial images, distal branches of visceral arteries and femoral arteries can be seen, as well as aorta. **(a)** Superior mesenteric artery and hepatic artery can be seen. **(b)** Superior mesenteric artery branch can be seen. **(c)** Common femoral arteries can be seen. **(d)** Not an enough quality for volume rendered image.

TA-CTA: Transarterial computed tomography angiography; EVAR: Endovascular aortic aneurysm repair.

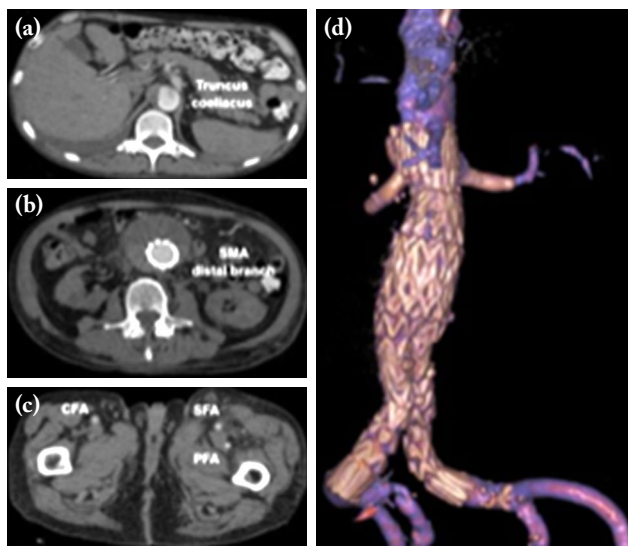

Figure 2. An example for IQS 3. TA-CTA images which was performed on a 65-year-old man with an abdominal aortic aneurysm and chronic kidney disease after EVAR. On axial images, distal branches of visceral arteries and femoral arteries can be seen, as well as aorta, but only proximal segments of visceral arteries and iliac arteries are seen, as well as aorta, on the axial and volume rendered images. **(a)** Truncus coeliacus and its branches can be seen. **(b)** Superior mesenteric artery and its distal branches can be seen. **(c)** Common femoral arteries and its branches can be seen. **(d)** Only proximal segments of visceral arteries and iliac arteries can be seen on volume rendered images.

TA-CTA: Transarterial computed tomography angiography; EVAR: Endovascular aortic aneurysm repair.

IQS 2. The mean IQS of Observer 1 was 3.52 and of Observer 2 was 3.47. Only one TA-CTA procedure was scored differently. The intra-observer agreement was 94% (Figure 1 and 2).

Among four thoracoabdominal TA-CTA procedures, in which 16 mL of contrast agent was used, three had IQS 4 and one had IQS 2. Among 13 abdominal TA-CTA procedures, in which 8 mL of contrast agent was used, six had IQS 4, five had IQS 3, one had IQS 2, and one had IQS 3.5. There was no statistically significant difference in the mean IQS between the 8 mL and 16 mL groups. The IQS of both observers, the mean IQS, the amount of contrast agent used, and aneurysm types are summarized in Table 4.

Of nine TA-CTA procedures performed for control purposes after EVAR, only one procedure had type 2 endoleak, which was detected by both observers. On CDUS performed after EVAR, type 2 endoleak was detected in the same patient. No endoleak was detected on TA-CTA or CDUS in the remaining procedures.

The mean baseline serum creatinine values were 2.35 (range, 1.34 to 4) mg/dL and the mean baseline eGFR values were 32.2 (range, 16.1 to 56.3) mL/min/1.73 m^2. The highest serum creatinine levels on Days 2-5 and at Months 1-3 was 2.27 (range, 1.2 to 4.4) mg/dL and 2.28 (range, 1.3 to 4.1) mg/dL, respectively. The lowest eGFR values on Days 2-5 and at Months 1-3 were 34.2 (range, 14.4 to 64) mL/min/1.73 m^2 and 34.6 (range, 15.6 to 58.3) mL/min/1.73 m^2, respectively. No significant difference was found in the baseline serum creatinine and eGFR values between the highest serum creatinine values on Days 2-5 and at Months 1-3 and the lowest serum eGFR values on Days 2-5. However, there was a statistically significant difference in the baseline eGFR values and the lowest eGFR values at Months 1-3 and this difference was also seen in the eGFR values. All kidney function test results before and after the procedures are presented in Table 5.

None of the patients had a serum creatinine level of ≥25% on Days 2-5 compared to baseline

TABLE 4
Aneurysm types, amount of contrast material used, and image quality scores

No	Type of aneurysm	Contrast amount used (mL)	Observer 1 Image quality score	Observer 2 Image quality score	Mean image quality score
1	Abdominal	8	4	4	4
2	Abdominal	8	4	4	4
3	Abdominal	8	3	3	3
4	Thoracoabdominal	16	2	2	2
5	Thoracoabdominal	16	4	4	4
6	Abdominal	8	2	2	2
7	Thoracoabdominal	16	4	4	4
8	Abdominal	8	4	4	4
9	Abdominal	8	4	4	4
10	Abdominal	8	4	3	3.5
11	Abdominal	8	3	3	3
12	Thoracoabdominal	16	4	4	4
13	Abdominal	8	4	4	4
14	Abdominal	8	3	3	3
15	Abdominal	8	4	4	4
16	Abdominal	8	3	3	3
17	Abdominal	8	4	4	4
Mean	-	9.88	3.52	3.47	3.495

TABLE 5
Lowest serum creatinine and eGFR values before the procedure, on Days 2-5, and at Months 1-3 after the procedure

No	Basal Cre and e-GFR values (mg/dL; mg/min/1.73 m^2)	Lowest Cre and highest e-GFR values on Days 2-5 (mg/dL; mg/min/1.73 m^2)	Lowest Cre and highest e-GFR values on Months 1-3 (mg/dL; mg/min/1.73 m^2)
1	2.80/22.7	2.76/23.1	2.80/22.7
2	2.86/23.1	2.81/23.6	2.41/24.2
3	2.52/27.4	2.18/32.3	2.93/25.8
4	2.47/28.7	2.82/24.7	2.44/29.1
5	3.00/23.0	2.88/24.1	2.57/27.5
6	1.96/27.3	1.98/25.4	1.62/32.0
7	1.38/55.0	1.40/54.4	1.30/58.9
8	2.00/33.3	1.70/42.4	1.67/43.3
9	1.67/43.3	1.49/49.1	1.53/54.9
10	2.19/31.5	1.82/39.0	2.05/34.0
11	2.46/27.4	2.30/29.6	2.11/32.7
12	1.84/37.4	1.68/41.5	1.79/38.6
13	1.37/53.3	1.44/50.3	1.35/54.0
14	2.84/22.9	2.64/24.9	3.40/18.7
15	3.39/18.7	3.22/19.8	3.40/18.7
16	4.00/16.1	4.40 /14.4	4.10/15.6
17	1.34/56.3	1.20/64.0	1.30/58.3
Mean	2.35/32.2	2.27/34.2	2.28/34.6

eGFR: Estimated glomerular filtration rate.

indicating CIN. A mild decrease was detected in the mean serum creatinine values of 12 procedures. Also, there was a statistically significant difference in the comparison of baseline eGFR values with the lowest eGFR values at Months 1-3. The decrease in serum creatinine values and the difference in eGFR levels was related to the hydration before and after the procedure, NAC treatment, discontinuation of possible nephrotoxic drugs, and the precautions taken to prevent CIN.

Furthermore, there was no statistically significant difference in the evaluation of 8 and 16 mL of contrast agents on the kidney function tests at four different time points (on Days 2-5 and at Months 1-3). All measurements are given in Tables 6 and 7.

DISCUSSION

Radiological imaging studies are needed for follow-up and treatment decision of an aortic aneurysm, which is a disease with a high mortality rate.[5] These radiological imaging modalities should be three-dimensional with a high spatial resolution and contrast enhancement to be used in the decision making of surgical or endovascular treatment methods. In particular, the morphological eligibility criteria of the aneurysms for EVAR procedure should be evaluated, which has been increasingly preferred recently to surgical procedures.

The CTA is a worldwide approved standard method used in the planning and follow-up of endovascular treatment.[1,2] It is well known that contrast agents used in CTA are nephrotoxic and tend to lead to CIN; therefore, morbidity and mortality rates increase leading to longer hospitalization duration and increased medical expenses.[6,7] Patients with aortic aneurysms are more often elderly having other comorbidities. Diabetes mellitus and renal injury are the most common comorbidities in these patients.[5]

TABLE 6
P values obtained from the comparison of baseline serum creatinine and eGFR values with highest serum creatinine and lowest e-GFR values on Days 2-5 and at Months 1-3

1. Parameter	Basal serum creatinine values	Basal serum creatinin values	Basal e-GFR values	Basal e-GFR values
2. Parameter	Highest serum creatinine values on Days 2-5	Highest serum creatinine values on Months 1-3	Lowest e-GFR values on Days 2-5	Lowest e-GFR values on Months 1-3
P value	0.084	0.109	0.061	0.017

eGFR: Estimated glomerular filtration rate.

TABLE 7
P values obtained from the comparison of the changes on renal function of 8 mL and 16 mL of contrast material

1. Parameter	The effect of 8 mL contrast material on creatinine at Days 2-5	The effect of 8 mL contrast material on creatinine at Months 1-3	The effect of 8 mL contrast material on e-GFR at Days 2-5	The effect of 8 mL contrast material on e-GFR at Months 1-3
2. Parameter	The effect of 16 mL contrast material on creatinine at Days 2-5	The effect of 16 mL contrast material on creatinine at Months 1-3	The effect of 16 mL contrast material on e-GFR at Days 2-5	The effect of 16 mL contrast material on e-GFR at Months 1-3
P value	1.00	0.624	0.785	0.412

eGFR: Estimated glomerular filtration rate.

The most important reason for CIN is impaired kidney functions, and another significant risk factor is the amount of contrast agent used.[3,4] Patients with aortic aneurysms are exposed to large amounts of contrast agent during treatment planning, during EVAR, and during follow-up after EVAR. This condition also carries a high risk for the development of CIN in patients with CKD and aortic aneurysms. Thus, alternative imaging methods to CTA are needed to consider in these patients.

All these limitations led us to seek an easy applicable, operator-independent technique which can be used in CKD patients before and after EVAR with a high resolution and sufficient anatomical details and without aggravating the already impaired renal functions or causing new renal injuries. In the present study, we used the TA-CTA technique to overcome these limitations. We obtained sufficient IQS (mean: 3,495) from all 17 TA-CTA procedures. None of the patients developed procedure-related contrast material nephrotoxicity or complications. In 12 procedures, the mean creatinine levels on Days 2-5 after the procedure were lower than the baseline levels, which can be related to the precautions taken to decrease CIN, particularly adequate hydration (saline, sodium bicarbonate infusions) before and after the procedures, erythropoietin treatment in patients with renal anemia (hemoglobin values below 11 g/dL, erythrocyte suspension was replaced), avoiding the unnecessary use of loop diuretics, antibiotics and nonsteroidal anti-inflammatory drugs, discontinuation of angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers 24 h before the procedure, preventing hypotension and dehydration, and continuation of regular statin use. There are many studies suggesting that, beside the use of low-dose contrast material, hydration is the most important measure in the protection from CIN.[8] The comparison of baseline serum creatinine and eGFR values with post-procedural short- and long-term serum creatinine and eGFR values showed a significant difference in favor of eGFR values only between baseline and at Months 1-3.

To the best of our knowledge, there is no study similar to ours concerning EVAR planning and follow-up with the use of very low contrast material. However, in a similar study including eight patients with CKD, Isaacson et al.[9] reported that that low-dose iodine TA-CTA was a feasible option for EVAR planning. Also, Joshi et al.[10] used an intra-arterial low-dose contrast agent with CTA in the evaluation of pelvic blood vessels of patients with renal insufficiency

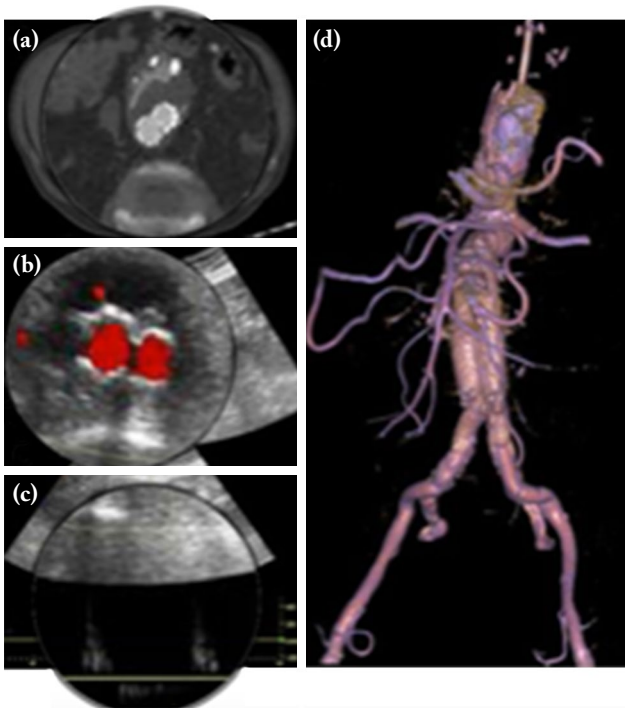

Figure 3. An example for type 2 endoleak and IQS 4. TA-CTA and CDUS images performed on an 80-year-old man with an abdominal aortic aneurysm and chronic kidney disease after EVAR. **(a-c)** Type 2 endoleak can be seen easily in both of axial images, CDUS images, and its spectral analysis. **(d)** Distal branches of visceral arteries and femoral arteries are seen, as well as aorta on the axial and volume rendered images.

TA-CTA: Transarterial computed tomography angiography; EVAR: Endovascular aortic aneurysm repair; CDUS: Color Doppler ultrasound.

undergoing percutaneous aortic valve replacement and they mixed normal saline and 10 to 15 mL of contrast agent with a ratio of 3:1 and 4:1 and, then, injected the mixture through a pigtail catheter which was inserted into the abdominal aorta at the infrarenal level. Prior to the intraarterial CTA, they performed pelvic digital subtraction angiography to ensure the catheter level. The mean baseline eGFR values before the procedure was 54.8±3.9 mL/min/1.73 m^2. The authors conclude that there was no significant difference in the eGFR values before and 72 h after the procedure. In our study, we successfully scanned a larger area with the use of less contrast material (8 and 16 mL) after we placed the flush catheter and also lowered the additional contrast load by avoiding angiography. Furthermore, the mean baseline eGFR value in our patient group was 32.2 mL/min/1.73 m^2, indicating a much lower value.

For the thoracoabdominal and abdominal TA-CTA, we used 16 mL and 8 mL of contrast agent, respectively. There was no statistically significant difference in the renal functions or the IQS between the two doses. However, the non-significant difference between 8 mL and 16 mL contrast agent can be attributed to the length of the area scanned. The non-significant difference on renal functions between the two doses suggests that 16 mL of contrast agent can be safely used in TA-CTA with a better image quality.

The insufficient amount of contrast used in the detection of type 2 endoleak caused by retrograde reflux after EVAR in control patients may be a limitation to the present study. To eliminate this deficit, we performed additional CDUS on the control group after EVAR. Type 2 endoleak was detected in only one patient by CDUS. The endoleak detected on CDUS was also clearly visible on TA-CTA (Figure 3).

In general, the amount of contrast agent used during EVAR is very high. It would be appropriate to lower the use of contrast during imaging methods and to use techniques that would lower the amount of contrast used during procedures in CKD patients, as in our study. For this purpose, among the endovascular abdominal aortic repair methods, stenting and renal artery catheterization technique with carbon dioxide (CO_2) has come to the forefront.[11] The CO_2 is a gas with negative contrast features. Aortic stent procedure with CO_2 is a safe and successful method. Due to the low contrast resolution of CO_2, special post-processing software and automatic gas injectors providing continuous gas infusion are necessary.[12] Aortic stent procedure takes longer; therefore, the amount of radiation received increases. The most important theoretical risks are stroke and ischemia of the spinal cord in supradiaphragmatic use.[13] In addition to being an inexpensive negative contrast material, there is no CO_2 tube regulator system for pressure regulation during injection in Turkey and, therefore, its use is not widespread in our country.

In a study conducted by Canyigit et al.,[14] the renal artery catheterization technique was used in 16 patients with impaired renal functions, and no significant difference was found in the serum creatinine and eGFR values before and 72 h after the procedure. The technique is based on catheterization of the renal artery with Simmons catheter without the use of contrast and the renal artery level is localized without the use of aortography. Thus, the use of high amount of contrast

material for the detection of renal artery level during EVAR and the repeated use of aortographies for distance determination while first placing the stent is not required. In the aforementioned study, the lowest possible amount of contrast material was used and the procedure was completed. The risk of CIN was minimized by intravenous hydration before and after the procedure. Of note, in CKD patients with aortic aneurysms, the use of lowest possible contrast dose is of utmost importance during diagnosis, treatment, and follow-up to minimize the risk of CIN.

Main limitation in our study was the low number of patients.

In conclusion, the TA-CTA obtained with diluted low-dose contrast material in CKD patients with an aortic aneurysm is an invasive, but safe and easy-to-use method which provides sufficient anatomical details without causing CIN risk. Further large-scale, prospective studies are needed to confirm these findings.

Declaration of conflicting interests

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Comparison of septal myectomy and transcoronary septal alcohol ablation in patients with hypertrophic obstructive cardiomyopathy

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ABSTRACT

Objectives: This study aims to compare the efficacy of septal myectomy (SM) and septal alcohol ablation (SAA) for the relief of the left ventricular outflow tract (LVOT) gradient in patients with symptomatic hypertrophic obstructive cardiomyopathy (HOCM).

Patients and methods: Between January 2005 and January 2010, a total of 45 patients (32 males, 13 females; mean age 51.5 years; range, 17 to 87 years) with symptomatic drug-refractory obstructive HOCM were consecutively enrolled. The patients were divided into two groups as SM (n=17) and SAA (n=28). All patients underwent clinical and echocardiographic examinations before, during the procedure, and at the end of one-year follow-up.

Results: There was no significant difference in clinical and demographic characteristics of the patients who underwent SM and SAA. The mean LVOT gradients early after the procedures significantly decreased (p<0.001). At the end of one year, the mean maximal gradients in LVOT after exercise were similar (54±39 mmHg for SM and 73±53 mmHg for SAA; p=0.220).

Conclusion: Although SM is considered the preferred treatment in patients with HOCM, SAA may be an alternative approach to SM in the LVOT gradient reduction in experienced centers for high-risk surgical patients.

Keywords: Hypertrophic cardiomyopathy, myectomy, obstruction, septal alcohol ablation.

Hypertrophic obstructive cardiomyopathy (HOCM) is a heterogeneous cardiac disease with a wide spectrum of clinical presentations such as sudden cardiac death, presenting in all age groups from infancy to the very elderly.[1,2] Although septal myectomy (SM) has been regarded as the gold standard therapy, septal alcohol ablation (SAA) emerged as an attractive alternative for the treatment of HOCM. In patients with HOCM, the first-line medical therapy consists of beta-blockers, calcium channel blockers, and disopyramide which can adequately control symptoms. In case of refractoriness to optimal medical therapy, mechanical relief of the outflow tract obstruction choice is considered.

The Morrow operation is the classic myectomy technique which relieves obstruction by resection of a 2 to 5 g amount of muscle from the proximal ventricular septum.[3] The main goal of the procedure is to widen the outflow tract and, therefore, to abolish the Venturi effect and gradient reduction caused by systolic contact between mitral valve and hypertrophied septum.[3] By surgical relief of obstruction, the quality of life is improved, and long-term survival is equivalent to general population.[4,5] Likewise, for the same purpose, SAA can be performed with a percutaneous catheter; dehydrated ethanol, usually at a total dosage of 1 to 3 mL is, then, injected slowly through the proximal septal branches of the left anterior descending coronary artery, causing a targeted myocardial infarction.[6]

In the literature, no conclusive data on the effect of either SAA or SM on long-term survival are available. Previous studies have shown no difference in all-cause mortality or sudden death risk for patients with SAA compared to those undergoing myectomy

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or the general population in the short-term.[7] In this study, we aimed to compare the efficacy of these two treatment modalities, SM and SAA, on the relief of the left ventricular outflow tract (LVOT) gradient in patients with HOCM.

PATIENTS AND METHODS

Between January 2005 and January 2010, a total of 45 patients (32 males, 13 females; mean age 51.5 years; range, 17 to 87 years) with symptomatic drug-refractory obstructive HOCM were consecutively included in this study. The patients were divided into two groups as SM (n=17) and SAA (n=28). The clinical indication for SM and SAA was a LVOT gradient of >50 mmHg at rest or with provocation and New York Heart Association (NYHA) functional Class III or IV symptoms refractory to maximal medication as indicated in the current guidelines.[8] The patients with ventricular septal defect after SM and atrioventricular block, which is a common complication of SAA, or patients died during the hospitalization period immediately after the procedure were excluded. For all patients, the clinical and transthoracic echocardiography examinations were performed before, during the procedure, and at the end of the one-year follow-up. A written informed consent was obtained from each patient. The study protocol was approved by the Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

SM procedure

Septal myectomy is resection of a rectangular portion of a myocardium via two parallel incisions in the basal septum extended distally to beyond the level of mitral-septal contact and subaortic obstruction performed through an aortotomy after cold blood cardioplegia. The residual mitral valve regurgitation is almost always caused by intrinsic mitral valve abnormalities such as ruptured chordae, myxomatous degeneration with prolapse, or annular dilatation and can be corrected by direct valve repair. The transesophageal echocardiography was performed in all patients to identify mitral regurgitation before and during the procedure.

SAA procedure

Septal alcohol ablation is an interventional technique in which 2 to 4 cm^3 of 96% ethanol is introduced into a septal perforator branch of the left anterior descending coronary artery to intentionally produce an infarction in the ventricular septum. The appropriate myocardial segment at basal septum was determined using contrast echocardiography. The ultimate resolution of obstruction requires several months of septal remodeling, leading to outflow tract widening and reduced systolic anterior motion of the mitral valve mimicking the pathophysiology of myectomy.[6,9]

Echocardiographic examination

Echocardiographic parameters were obtained using standard two-dimensional and M-mode of the Vivid 7 GE echocardiography device (GE Healthcare, Little Chalfont, UK). Parasternal long and short axis, apical four-chamber, and apical two-chamber images were used for the evaluation of the left ventricular (LV) and valve functions. Pulsed Doppler ultrasound examination was performed with a 2.5 MHz transducer. Ejection fraction (EF), maximum gradient of LVOT, septal thickness, end-systolic and diastolic diameter of the LV, left atrial diameter, mitral regurgitation grade, and systolic anterior motion (SAM) were assessed separately.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 24.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. To compare baseline characteristics, the Mann-Whitney and Wilcoxon non-parametric tests or t-test were used for continuous variables, while the Pearson chi-square test was used for categorical variables. A p value of <0.05 was considered statistically significant.

RESULTS

There was no statistically significant difference in the baseline demographic and clinical characteristics of the patients who underwent SM and SAA (p=0.973) (Table 1).

The mean diastolic diameters of the LV of the patients were similar for SM and SAA procedure (4.6±0.8 mm and 5.0±0.4 mm, respectively; p=0.498). Also, there was no significant difference between the mean systolic diameter of the LVs (2.9±0.5 mm for SM and 3.0±0.7 mm for SAA; p=0.062). The diameters of the LA of the patients were also similar

Table 1
Baseline demographic and clinical data of patients

	SM group (n=18)			SAA group (n=28)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			51.4±18.1			51.5±13.4	0.973
Sex							0.123
Female	4	22		9	32		
Body mass index (kg/m^2)			27.3			26.9	0.865
New York Heart Association							
Class 3-4	3	16		3	10		0.701
Class 1-2	15	84		25	90		0.645
EuroSCORE II			1.2			1.4	0.893
History							
Coronary artery disease	3	16		5	17		0.843
COPD	1	5		2	17		0.625
Chronic kidney disease	1	5		4	14		0.325
Diabetes mellitus	3	16		5	17		0.863
Previous cardiac surgery	0	0		3	10		0.053
Family history	1	5		2	7		0.734
Echocardiography							
Ejection fraction (%)			61.8±6.4			59.3±6.5	0.221
LVOT max gradient (mmHg)			101±38.6			91.2±38.5	0.405
Septum thickness			2±0.4			1.9±0.2	0.652
LVEDD			4.6±0.8			5.0±0.4	0.498
LVESD			2.9±0.5			3.0±0.7	0.062
Left atrial diameter			4±0.3			3.7±0.5	0.104
Mitral regurgitation							
4-3	5	27		2	7		0.523
2-1	6	33		12	42		0.144
Systolic anterior motion	7	38		12	42		0.230

SM: Septal myectomy; SAA: Septal alcohol ablation; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; LVOT: Left ventricular outflow tract; LVEDD: Left ventricle end diastolic diameter; LVESD: Left ventricle end systolic diameter.

(p=0.104). There were no significant differences in the ejection fraction (EF) of the LV and the gradient of the outflow tract between the groups. The mean EF of the patients undergoing SM and SAA was 61±6.4% and 59±6.5%, respectively (p=0.221). The mean maximal LVOT gradient in the SM group was 101±38 mmHg and it was 91±38 mmHg in the SAA group (p=0.405).

The mean gradients early after the procedures significantly decreased and were also comparable between the groups of SM and SAA (40±28 mmHg and 43±34 mmHg, respectively; p=0.801). At the end

Table 2
Post-procedural data

	SM group (n=18)	SAA group (n=28)	
	Mean±SD	Mean±SD	*p*
Septum thickness (mm)	1.7±0.4	1.6±0.1	0.743
LVOT max gradient PP (mmHg)	40±28	43±34	0.801
LVOT max gradient (1 year) (mmHg)	54±39	73±53	0.220

SM: Septal myectomy; SAA: Septal alcohol ablation; SD: Standard deviation; LVOT: Left ventricular outflow tract; PP: Post-procedural.

of one year, the difference between the mean maximal gradients in LVOT were not statistically significant (54±39 mmHg for SM and 73±53 mmHg for SAA; p=0.220) (Table 2).

DISCUSSION

The clinical diagnosis of HOCM is conventionally made most commonly with two-dimensional echocardiography. In HOCM, the flow against the abnormally positioned mitral valve apparatus results in drag force on a portion of the mitral valve leaflets during ventricular systole which pushes the leaflets into the outflow tract. The outflow obstruction causes an increase in the LV systolic pressure, leading to prolongation of ventricular relaxation and, thus, elevation of LV diastolic pressure, mitral regurgitation, myocardial ischemia, and decrease in cardiac output eventually.[10,11]

Although there are no randomized trials comparing SM and SAA in the literature, several meta-analyses have shown that both procedures improve functional status with a comparable procedural mortality rate.[12] In the present study, we compared the systolic gradient of the LVOT in the patients who underwent SM versus SAA using two-dimensional transthoracic echocardiography. According to our study, although the differences at the mean gradient of LVOT between the SM and SAA increased from early after procedures to one year later, these differences were not statistically significant.

However, it is important to show that each technique does not give as much harm, as it is useful or induce new problems due to the procedure. Magnetic resonance imaging studies have demonstrated that SAA infarct may be both transmural and extensive.[13] In SM, unlike SAA, distribution of septal perforator coronary arteries for which precise targeting of the septum that contribute to mechanical LV outflow obstruction can be visualized by the surgeon. However, it has been suggested that the alcohol-induced scar does not represent a true infarction due to its chemical origin, rather than ischemic, and controlled size.[6]

While deciding the most optimal treatment choice of the HOCM, SM, rather than SAA, is recommended in patients with an indication for septal reduction therapy and other indications requiring surgical intervention (e.g., mitral valve repair/replacement, papillary muscle intervention) as a Class I indication by the European Society of Cardiology (ESC) guidelines.[8] Mitral regurgitation is usually present caused by the apposition of the anterior leaflet of the mitral valve through the bulging of the thickened septum of the LVOT during systole, namely systolic anterior motion. In this study, the presence of systolic anterior motion and mitral regurgitation were found to be associated with the higher gradient of LVOT in each procedure. Not surprisingly, in this group patients, the LA volume index was also higher.

The appropriate selection of patients for treatment procedure is an important predictor of outcome and should be individualized. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend the decision to proceed with SAA in advanced age, in the presence of a significant comorbidity which selectively increases the surgical risk, (e.g., significant concerns about lung or airway management), and in case of the patient's strong desire to avoid open heart surgery after a thorough discussion of both options.[14] Due to the absence of a surgical incision and general anesthesia, SAA has the potential for greater patient satisfaction. Besides less overall discomfort, SAA recovery time is also shorter. Due to the variable septal artery anatomy in each case, which may not supply the targeted area of the septum in up to 20 to 25% of patients, SAA may have hemodynamic and symptomatic improvement compared to SM, if the area of the systolic anterior motion-septal contact can be accessed by the first septal perforator and ablated.[15] After the procedure, a decrease in resting and provocable gradients usually occurs immediately; however, due to stunning, remodeling can result in continued gradient reduction over the first three months following the procedure. In our study, we showed the gradient reduction early after surgery and at the first year of the procedure. At the end of the first year, there was no statistically significant difference in the maximal gradient of the LVOT of the patients between the procedures.

It has been suggested that at least 50 successful procedures are required to overcome the SAA learning curve. If the patient who is either a good candidate for SM or SAA, a shared decision-making approach should be used to provide the patient all available data on the advantages and disadvantages of both strategies.

In patients with a septal thickness of <15 to 18 mm, SM poses a risk for ventricular septal defect.

Also, atrioventricular block is a common complication of SAA. In our study, we included the patients with successfully treated by SM or SAA without any complication. We also believe that systematic long-term follow-up studies are necessary to evaluate whether alcohol-induced myocardial infarction or SM poses an increased risk for ventricular arrhythmias of sudden death.

In conclusion, although the surgical SM is considered the preferred treatment in patients with HOCM, SAA may be an alternative approach to SM in the LVOT gradient reduction in experienced centers for high-risk surgical patients.

Declaration of conflicting interests

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Is primary closure still a reliable technique in carotid endarterectomy?

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ABSTRACT

Objectives: This study aims to evaluate perioperative and long-term results of carotid endarterectomy (CEA) in terms of primary closure and patch techniques.

Patients and methods: This retrospective study included a total of 289 patients (145 males, 144 females; mean age 64.9±3.85 years; range, 53 to 84 years) who underwent elective CEA in our clinic between January 2014 and January 2019. The patients were divided into two groups as Group 1 consisting of patients who received patch closure (n=62) and Group 2 consisting of patients who received primary closure (n=227). Both groups were compared in terms of demographic and clinical data, and postoperative results.

Results: There was no significant difference between the groups in terms of demographic characteristics. The mean cross-clamp time was significantly shorter in Group 2 (p=0.001). The rate of hematoma formation was higher in Group 1 (p=0.048), while acute myocardial infarction (p=0.431), stroke in the short-term (p=0.839) and long-term (p=0.429), development of restenosis ≥70% (p=0.839), and mortality rates (p=1.0) did not differ significantly between the groups.

Conclusion: Our study results indicate that the application of patch or primary closure techniques during CEA has no significant superiority to each other in the early- and mid-term. In eligible cases and in whom the arterial diameter is over 5 mm, primary closure can be performed safely.

Keywords: Carotid endarterectomy, hematoma, patch closure, primary closure, restenosis.

Carotid endarterectomy (CEA) reduces the risk of cerebrovascular ischemic events. Additionally, it is effective in preventing recurrent stroke in patients with symptomatic carotid artery stenosis (CAS) and postoperative stroke with a mortality rate below 3%.[1,2] Currently, CEA is the gold-standard treatment modality for severe CAS.[3] One of the controversial issues regarding CEA is the closure technique of arteriotomy after CEA. In primary closure, 1 to 36% restenosis ratio requires the development of alternative methods and, therefore, the European Society for Vascular Surgery (ESVS) guidelines recommend patch closure after CEA.[4-6] This proposal is based on the Cochrane Collaboration in 2009, which was updated in 2011, and dates back approximately to 20 years.[7,8] According to the existing data, patch angioplasty closure reduces the risk of perioperative stroke, restenosis, and long-term ipsilateral ischemic stroke.[7,8] It has been reported that the rate of postoperative stroke and death reduce and, with the advance of technology and modern practices, 3 to 7%.[4,9-12] In recent studies including the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) and National Surgical Quality Improvement Program (NSQIP) data, there were no significant differences in the rates of postoperative restenosis, stroke, and death between these two methods.[11,13-15]

In the current study, we aimed to evaluate perioperative and long-term results of CEA in terms of primary closure and patch techniques.

PATIENTS AND METHODS

This retrospective study included a total of 289 patients (145 males, 144 females; mean age 64.9±3.85 years; range, 53 to 84 years) who underwent elective CEA in our clinic between January 2014 and January 2019. The patients were divided into two

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groups as Group 1 (n=62) receiving patch closure and Group 2 (n=227) receiving primary closure. Patients who received a concurrent operation with CEA, such as neck procedures or open heart surgery were excluded from the study. Baseline demographic and clinical characteristics and peri- and postoperative complications were recorded. If there was severe CAS (>70%) in symptomatic or asymptomatic patients, the patients were evaluated by the Neurology and Cardiovascular Surgery Council, and the operation decision was taken. A written informed consent was obtained from each patient. The study protocol was approved by the Eskişehir Osmangazi University Faculty of Medicine Ethics Committee (No. 2019-319). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Surgical procedure

All patients were operated under general anesthesia and their systolic arterial blood pressures were invasively monitored and kept at a level of 140 to 160 mmHg. A patch was used where the internal carotid artery (ICA) diameter was less than 5 mm and/or if the stenosis extended to the distal of ICA. None of the patients needed a shunt. Under near-infrared spectroscopy (NIRS), the carotid arteries were exposed and suspended. Before clamping the arteries, 100 IU/kg heparin was administered intravenously. A longitudinal incision was made to extend to the ICA, and the plaques within the ICA, external carotid artery (ECA), and common carotid artery (CCA) were removed with a dissector.

After the full opening was achieved in Group 1, the saphenous vein was prepared and trimmed as a patch. This patch was used for closure of the carotid incision. On the other hand, in Group 2, the incision was closed with a continuous suturing method using 6/0 propylene. A mini-drain was placed in all patients, and the subcutaneous areas and skin were closed with an absorbable polyglactin stitches. All the patients were extubated at the operating room. The patients were, then, taken to the intensive care unit and followed with an appropriate dose of heparin infusion after arterial blood pressure regulation.

The patients received combined antiaggregant medical therapy (acetylsalicylic acid 100 mg and clopidogrel 75 mg) as of the postoperative Day 1. If the patients needed an anticoagulant therapy due to atrial fibrillation, previous mechanical heart valve replacement, or previous deep vein thrombosis, they were prescribed acetylsalicylic acid 100 mg and warfarin at appropriate doses (international normalized ratio [INR]: 2,5-3). The patients were transferred to the ward in the first postoperative day provided that their general condition was stable.

All patients were followed for one year. Control Doppler ultrasonography was performed at one, six, and 12 months after surgery for all patients. If there was stenosis over 50% on Doppler ultrasonography, computed tomography angiography (CTA) was performed. The diagnosis of restenosis was made based on CTA results.

Statistical analysis

Statistical analysis was performed using the PSPP version 1.2.0 software (Free Software Foundation, Inc., MA, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The Pearson chi-square (including continuity correction) and Fisher's exact test were used to compare categorical data between the groups. A p value of <0.05 was considered statistically significant.

RESULTS

Baseline demographic and clinical characteristics of the patients are summarized in Table 1. Of a total of 289 patients who underwent CEA, primary closure was performed in 227 patients and patch angioplasty in 62 patients. There was no statistically significant difference in the baseline demographic data between the patient groups. However, the mean cross-clamp time was 30.4±3.8 min in Group 1 and 20.7±2.5 min in Group 2 (p<0.001), indicating significantly shorter time in the primary closure than the patch closure technique.

A total of 11 patients underwent postoperative neck exploration due to surgical site hematoma, 8.1% (n=5) in Group 1 and 2.6% (n=6) in Group 2 (p=0.048). The incidence of surgical site hematoma was statistically higher in Group 1. Immediate-term stroke rate after surgery was 1.6% (n=1) in Group 1 and 3.1% (n=7) in Group 2. Except for the early postoperative period, stroke was seen at one week (1.3%, n=3) and one year (2.6%, n=6) in only Group 2. There was no statistically significant

Table 1
Baseline demographic and clinical characteristics of patients

Variable	Group 1 (n=62) n	%	Mean±SD	Group 2 (n=227) n	%	Mean±SD	*p*
Age (year)			64.2±3.5			65.1±3.9	0.087*
Sex							
Male	26	41.9		119	52.4		0.143†
Family history	4	6.5		12	5.3		0.966‡
Smoking	28	45.2		110	48.5		0.645†
Diabetes mellitus	10	16.1		30	13.2		0.556†
Systemic hypertension	17	27.4		77	33.9		0.333†
Coronary artery disease	6	9.7		23	10.1		0.916†
Peripheral artery disease	6	9.7		16	7		0.489†
Cerebrovascular accident	13	21		51	22.5		0.801†
Bilateral carotid endarterectomy	8	12.9		32	14.1		0.809†
Clamp time (min)			30.4±3.8			20.7±2.5	<0.001*

SD: Standard deviation; * Independent-samples t-test; † Chi-square test; ‡ Fisher's exact test with continuity correction.

difference in the stroke rate between the groups. The rate of acute myocardial infarction (AMI) was 3.2% in Group 1 and 0.9% in Group 2. The mortality rate was 0.4% in Group 2, while there was no mortality in Group 1. In addition, there was no significant difference in the complication rate, except for hematoma, between the groups. The postoperative results are presented in Table 2.

DISCUSSION

To date, the CEA studies have provided highly controversial results in terms of post-CEA closure techniques. The general view is that the patch closure method minimizes the risk of perioperative and long-term stroke and restenosis, compared to the primary closure method; however, the existence of

Table 2
Postoperative outcomes

	Group 1 (n=62) n	%	Group 2 (n=227) n	%	*p*
Acute myocardial infarction	2	3.2	2	0.9	0.431†
Hematoma	5	8.1	6	2.6	0.048*
Stroke (immediate-term)	1	1.6	7	3.1	0.850‡
Stroke (1st week)	0	0	3	1.3	0.839‡
Stroke (1st year)	0	0	6	2.6	0.429‡
TIA (immediate-term)	3	4.8	5	2.2	0.494‡
Restenosis (50-70%)¶	3	4.8	5	2.2	0.494‡
Restenosis (≥70%)¶	0	0	3	1.3	0.839‡
Mortality¶	0	0	1	0.4	1.0‡

TIA: Transient ischemic attack; * Independent-samples t-test; † Chi-square test; ‡ Fisher's exact test with continuity correction; ¶ Indicates restenosis rates at postoperative first year.

controversial results requires more studies to support these findings.[7,8,16-18] There is still no consensus among the surgeons about the closure technique and, therefore, each surgeon decides on the closure technique based on his or her own experience. In the present study, we found no statistically significant difference in the perioperative results, except for hematoma, between the two groups.

In previous studies, the effects of closure techniques in CEA on complications developed after surgery were studied. In a meta-analysis conducted in 2,157 patients, the patch closure technique was associated with a significant reduction in perioperative ipsilateral stroke and ICA thrombosis within 30 days.[19] Besides, in the long-term, late ipsilateral stroke and ICA restenosis rates reduced in patients undergoing patch closure technique. However, there was no significant difference between the primary and patch closure techniques in terms of perioperative and stroke-related mortality. Similarly, another study reported lower restenosis rates compared to primary closure after patch procedure.[20] In addition, patients undergoing patch closure had a lower rate of restenosis within two years after CEA.[21] In this study, restenosis rates were slightly higher in Group 2, although not statistically significant. This result can be attributed to the patient selection criteria used in the study.

In the first Cochrane review published in 2009 and which was updated in 2011, there was no significant difference between the two closure methods in the perioperative period; however, the patch closure method was reported to reduce stroke and restenosis rates in the long-term.[7,22] In a study in which the patch closure method was riskier than primary closure was emphasized, patients who received patch closure (12.9%) had an incidence of recurrent CAS compared to those with primary closure (1.7%).[23] In this study, the authors used venous patch material and, in case of using a saphenous vein, it did not show any superiority over primary closure in the long-term of five years. However, many other studies suggested that there was no significant difference between the two closure methods. In one of these studies, neither methods affected the occlusion or stroke rates.[23]

On the other hand, the primary closure method has several advantages compared to the patch closure method, including low risk of infection, fewer complications, and shorter operation and arteriotomy time.[13,14,18] Previous retrospective studies have shown that closure techniques do not affect perioperative and long-term postoperative results. In a study conducted using the American College of Surgeons (ACS) NSQIP database, closure techniques for CEA were not found to be associated with complications. On the contrary, one or more high-risk features such as preoperative stroke, age above 80 years, and active smoking were found to be predictors of 30-day postoperative stroke or death after CEA in patients having these risks.[14] In a very recent study conducted in South Korea, no significant difference in restenosis rates was observed in the perioperative period and long-term after patch and primary closure techniques in 435 patients.[24] In another study, there was no statistically significant difference in the restenosis rate in the mid-term between the patch closure and primary closure techniques.[25] This finding is also consistent with our study results. Some urgent CEAs were performed with primary closure for short cross-clamp time of carotid arteries.[26] Also, in our study, primary closure technique decreased clamping time, although there was no significant difference in the stroke rates in early- and mid-term.

Doppler ultrasonography can be useful in following patients after surgery for restenosis and preoperative risks.[27] In our study, we followed patients with Doppler ultrasonography after surgery. If there was stenosis over 50% on Doppler ultrasonography, we used CTA for these patients. Furthermore, although combined antiaggregant and anticoagulant therapy was administered in a study,[28] in our study, medical treatment was chosen for each case individually.

Nonetheless, there are some limitations to this study. Its retrospective and single-center design are the main limitations which preclude the generalization of the results. In addition, common opinions in choosing a closure technique for surgeons working in a single center may lead to a biased selection. Also, as perioperative data were not included in our study, postoperative results were further elaborated. Additionally, the duration of follow-up was relatively short (one year) and, thus, long-term follow-up is required for further evaluation and recommendation. Also, if the ICA diameter was below 5 mm, primary closure technique was not preferred, indicating a significant difference in the anatomical structure of the ICA between the two groups. We believe

that further large-scale, long-term, prospective, randomized studies would provide more robust data about the primary closure technique.

In conclusion, there was no significant difference between the primary and patch closure techniques in terms of AMI, short- and long-term stroke, transient ischemic attack, and long-term restenosis and mortality rates. Our study results suggest that the application of patch or primary closure techniques during CEA has no significant superiority to each other in the early- and mid-term. In eligible cases and in whom the ICA diameter is over 5 mm, primary closure can be performed safely.

Declaration of conflicting interests

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A comparison of modified eversion endarterectomy versus classical endarterectomy in the surgical treatment of carotid artery stenosis

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ABSTRACT

Objectives: In this study, we aimed to compare the modified eversion method versus classical carotid endarterectomy in the treatment of carotid artery stenosis.

Patients and methods: A total of 112 patients (85 males, 27 females; mean age 64.8±9.5 years; range, 40 to 82 years) who underwent carotid endarterectomy in our hospital between January 2009 and December 2011 were retrospectively analyzed. The patients were divided into two groups according to the method used as the modified eversion group (n=27) and classical endarterectomy group (n=85). Doppler ultrasound of 62 patients who could be reached among these patients were evaluated and compared in terms of early results of restenosis.

Results: There was no statistically significant difference between the two groups in terms of intraoperative morbidity, mortality, and complications. While there was no mortality in the modified eversion technique, postoperative subcutaneous hematoma occurred in one (3.7%) patient and revision was applied, and morbidity in the form of right hemiplegia was observed in another patient (3.7%). In classical endarterectomy, mortality was observed in four (4.7%) patients. One (1.2%) patient underwent subcutaneous hemorrhage revision, and morbidity in the form of right hemiplegia was observed in another patient (1.2%). There was no statistically significant difference between the two groups in terms of early results of restenosis. Severe stenosis was found in the arteries undergoing endarterectomy in one patient (4.8% vs. 2.4%) in each group.

Conclusion: The modified eversion method used in our clinic is as effective as classical carotid endarterectomy. This method should be considered an alternative to the classical endarterectomy technique.

Keywords: Carotid artery stenosis, endarterectomy, modified eversion technique.

In countries with ischemic stroke, it is the disease group that ranks third in terms of cause of mortality, while ranking the first in terms of long-term morbidity. Carotid artery stenosis (CAS) accounts for 20% of all ischemic strokes.[1] In symptomatic carotid artery patients with severe stenosis, carotid endarterectomy (CEA) is recommended as the primary treatment for the prevention of stroke and its complications,[2-5] as well as prioritized over other treatments in asymptomatic patients with severe stenosis.[6-8] There are differences between surgical techniques in CEA, which has such an important place in the treatment of carotid artery disease. In addition, there are differences in the same techniques such as whether to use shunts and whether to use patches (synthetic or native).

In the present study, we aimed to compare the modified eversion endarterectomy (MEE) and the classical CEA method, which are among the CEA methods performed in our hospital.

PATIENTS AND METHODS

The medical records of a total of 112 patients (85 males, 27 females; mean age 64.8±9.5 years; range, 40 to 82 years) who underwent CEA between January 2009 and December 2011 in our hospital were retrospectively analyzed. Data including age, sex, body mass index, smoking and alcohol use, diabetes, hypertension, hyperlipidemia, renal failure, contralateral carotid artery lesion, peripheral artery disease, coronary artery disease, previous

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cerebrovascular accident (CVA), operation type, postoperative CVA, use of shunt, and graft usage were recorded. Control carotid Doppler ultrasound (DUS) was performed in 62 patients who could be reached among this patient group. This examination was applied to each patient in the radiology department using the same Doppler device (Logic® 9 Color Duplex Scan; General Electric Medical Systems, WI, USA) with a 10-L probe by a single radiologist. Intraoperative cross-clamp time, graft and shunt usage, operative data, postoperative mortality and morbidity data of the patients were recorded. The patients were divided into two groups according to the method used as the MEE group (n=27) and classical CEA group (n=85).

A written informed consent was obtained from each patient. The study protocol was approved by the Kartal Koşuyolu Yüksek Ihtisas Training and Research Hospital Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Surgical technique

Classical CEA technique

Following appropriate disinfection and sterile covering under general anesthesia, with a vertical incision, an incision is made along the anterior medial line of the sternocleidomastoid muscle, from the two fingers above the clavicle to the corner of the chin. Dissection is continued subcutaneously along the medial of the sternocleidomastoid muscle. Then, the platysma is dissected. The internal carotid artery (ICA) is explored 3 to 5 cm distal from the bifurcation. The external carotid artery (ECA) is dissected up to 2 cm to distal and freed. If bradycardia occurs due to carotid body stimulation, 2-mL lidocaine is injected. After exploration, 100 IU/kg of intravenous heparin is administered to systemically heparinize the patient. The main carotid artery (MCA), ICA, and ECA are individually wrapped with rubber tapes. Firstly ICA, then ECA, and lastly MCA are clamped with the vascular clamp. The MCA is incised from the bifurcation toward the ICA with a No.11 scalpel. Arteriotomy is lengthened with the Potts scissors. Endarterectomy is performed using microsurgical dissectors by finding the plane between the atherosclerotic plaque and the vessel wall. The plaque is pulled to superior part in proximal direction, and the tunica-media separation is dissected and continued toward the ICA.

The plaque part, which extends toward the ECA, is dissected circumferentially by eversion and removed from the artery. Arteriotomy is closed with a 6/0 monofilament (prolene) using continuous suture technique. Before tying the suture knot, the ECA clamp is opened and closed, allowing air in lumen to escape. After tying the knot, first ECA, then MCA and lastly ICA clamps are taken, respectively. Once bleeding is controlled, 1 Hemovac drain is placed. The subcutaneous tissue and skin are closed properly.

Modified eversion endarterectomy technique

In this technique, the same method as in classical CEA is applied until MCA, ECA, and ICA clamping. After the cross-clamp, the incision extending from the common carotid artery (CCA) to the ICA is moved forward to the plaque, and the plaque is not opened. By proceeding from the plane between the plaque and the vessel wall as a whole, the plaque is removed first from the ECA, then the CCA, and finally the ICA by everting it. In this method, the lumen is not entered to and no shunt is used. The closure procedure can be made with a patch or primary incision, as in the classical CEA method. The order of air evacuation and lifting the cross-clamps before closing the last stitches is the same as in the classical CEA.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The Student's t-test was used in comparison of quantitative data to compare normally distributed parameters between the two groups. The chi-square test and Fisher's exact chi-square test were used to compare qualitative data between the groups. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 112 patients, the intraoperative results of both methods and early period restenosis results of 62 patients who attended to the follow-up visits were compared. While the MEE was applied to 27 (24.1%) patients, CEA method was applied to 85 (75.9%) patients. Baseline demographic characteristics of the patients are shown in Table 1.

According to the method used in the operation, there was no statistically significant difference between

Table 1
Baseline demographic characteristics of patients

	Modified eversion method (n=27)			Classical endarterectomy (n=85)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			60.4±11.0			67.4±8.3	0.001**†
Body mass index (kg/m^2)			26.3±4.7			28.1±3.7	0.044*†
Sex							0.800‡
Male	20	74.1		65	76.5		
Female	7	25.9		20	23.5		
Smoking	17	63.0		39	45.9		0.122‡
Alcohol use	3	11.1		7	8.2		0.702‡

SD: Standard deviation; † Student's t-test; ‡ Chi-square and/or Fisher's exact test; * p<0.05; ** p<0.01.

the rates of diabetes, hypertension, hyperlipidemia, chronic renal failure, presence of stenosis in the contralateral carotid artery, and other peripheral artery disease (p>0.05). According to the method used in the operation, there was no statistically significant difference between the incidence of coronary artery

Table 2
Additional diseases

	Modified eversion method (n=27)		Classical endarterectomy (n=85)		
	n	%	n	%	*p*†
Diabetes	7	25.9	35	41.2	0.154
Hypertension	19	70.4	64	75.3	0.611
Hyperlipidemia	11	40.7	39	45.9	0.640
Chronic renal failure	5	18.5	7	8.2	0.157
Presence of stenosis in the contralateral carotid artery	14	51.9	47	55.3	0.754
Presence of other peripheral artery disease	5	18.5	16	18.8	0.972
CAD					0.778
Absence	5	18.5	11	12.9	
Medical follow-up	8	29.6	27	31.8	
Stent implanted	2	7.4	10	11.8	
Pre-CABG performed	5	18.5	10	11.8	
Simultaneous CABG	7	25.9	27	31.8	
Previous CVA					0.354
Absence	17	63.0	40	47.1	
Presence (no sequelae)	5	18.5	23	27.1	
Presence (with sequelae)	5	18.5	22	25.9	
Other diseases					0.117
Absence	16	59.3	52	61.2	
Non-ischemic cardiac diseases	2	7.4	12	14.1	
Chronic lung diseases	5	18.5	8	9.4	
Other systemic diseases	2	7.4	8	9.4	
NICD + Chr. LD	2	7.4	0	0	
Chr. LD + OSD	0	0	4	4.7	
NICD + Chr. LD	0	0	1	1.2	

† Chi-square and/or Fisher's exact test; CAD: Carotid artery disease; CABG: Coronary artery bypass grafting; CVA: Cerebrovascular accident; NICD: Non-ischemic cardiac diseases; Chr. LDs: Chronic lung diseases; OSD: Other systemic diseases.

Table 3
Intraoperative data

	Modified eversion method (n=27)			Classical endarterectomy (n=85)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Degree of lesion (%)			0.8±0.1			0.8±0.1	0.490†
Cross-clamp time (min)			15.4±2.8			17.3±6.7	0.470†
Operation							0.784‡
Right carotid endarterectomy	11	40.7		29	34.1		
Left carotid endarterectomy	9	33.3		29	34.1		
CABG + endarterectomy	7	25.9		27	31.8		
Use of graft							0.425‡
Not used	25	92.6		70	82.4		
Native graft	1	3.7		6	7.1		
Artificial graft	1	3.7		9	10.6		
Use of shunt							0.001*
Used	0	0		30	35.3		
Not used	27	100		55	64.7		

SD: Standard deviation; CABG: Coronary artery bypass grafting; † Student's t-test; ‡ Chi-square test; * p<0.01.

Table 4
Intraoperative and early postoperative data

	Modified eversion method (n=27)		Classical endarterectomy (n=85)		
	n	%	n	%	*p*†
Perioperative results					0.365
Good	26	96.3	80	94.1	
Wound hematoma	1	3.7	1	1.2	
Discharged with sequela	1	3.7	1	1.2	
Exitus	0	0	4	4.7	
Early results (n=62)					0.263
Good	20	95.2	40	97.6	
Advanced stenosis	1	4.7	1	2.4	

† Chi-square and/or Fisher's exact test.

disease (p>0.05). According to the method used in the operation, there was no statistically significant difference between the rates of previous CVA (p>0.05) (Table 2).

There was no statistically significant difference between the mean lesion degrees according to the method used in the operation (p>0.05). Although the mean cross-clamp times were shorter in the MEE compared to the method used in the classical CEA, no statistically significant difference was found (p>0.05). There was no statistically significant difference between the graft use rates according to the method used in the operation (p>0.05). Since shunts were not used in the MEE, there was a statistically significant difference between the rates of shunt use between the groups (p<0.01) (Table 3).

There was no statistically significant difference between the intraoperative results according to the method used in the operation (p>0.05). While the results of the intraoperative period were good in 26 (96.3%) patients in the MEE group, subcutaneous hematoma occurred in one (3.7%) patient and treated by revision, while one (3.7%) patient was discharged with sequelae. This case with sequelae had contralateral CAS; CEA combined with coronary artery bypass grafting (CABG) was applied to the patient, and CEA was performed under deep hypothermia. The carotid ultrasound of the patient was normal. The

intraoperative results were good in 80 (94.1%) patients in the CEA group, while one (1.2%) patient developed subcutaneous hematoma which was treated by revision and one (1.2%) patient case was discharged with sequelae. Four (4.7%) patients died as a result of postoperative CVA. No graft was used in any of these cases. Shunt was used in the patient who was discharged with sequelae. Bilateral carotid arteries were normal on control carotid DUS. Only CEA was performed in one of the patients who died, and a combination of CEA and CABG was performed in the other patients. Endarterectomy was performed in these patients under deep hypothermia and no shunt was used. There was no statistically significant difference between early restenosis rates according to the method used in the operation ($p>0.05$). The early results were good in 20 (95.2%) patients in the MEE group, while only one (4.7%) patient had severe stenosis. The early results were also good in 40 (97.6%) patients in the classical CEA group, while severe stenosis was observed in one (2.4%) patient (Table 4).

DISCUSSION

The incidence of CAS is substantially high in the elderly population as in the other peripheral artery diseases. In the Rotterdam study, stenosis between 16 and 49% was found in 3% of patients over the age of 55 years, and stenosis over 50% was found in 1.4%.[9] Similarly, in the Tromso study, the prevalence of CAS in men over the age of 50 years was found to be 4.2, while it was 2.7% in women, indicating a statistically significant difference between the sexes.[10] In the Framingham study, in 40% of 75-year-old men, a narrowing of more than 10% was found.[11] The disease, which is very widespread in the elderly, has a high cost to the society, the individual, and the environment. Considering the monetary cost, the total annual cost of stroke in the United States is estimated as $ 65.5 billion.[12] The total annual cost of stroke in the Europe is estimated as € 27 billion.[12] Carotid artery disease is the cause of an average of 20% of these strokes.

The necessity of the CEA method in advanced CAS, its priority over other treatment modalities, and the variety of surgical techniques applied urge us to find the most ideal surgical method. Before starting CEA, it is necessary to decide the anesthesia type of the operation. The randomized Local Anesthesia versus General Anesthesia for Carotid Surgery (GALA) study showed no significant difference between the general (4.8%) and local (4.5%) anesthesia in terms of intraoperative mortality, stroke or myocardial infarction.[13] In our clinic, general anesthesia method is routinely used. Since the arteriotomy performed in classical CEA includes CCA and ICA and the wide area can be reached in the CEA procedure, there is no problem in accessing the distal and proximal ends. However, there may be problems in finding the correct plane during the CEA procedure. The plaque may rupture in pieces rather than as a whole, leading to weakening of the vessel wall in some areas, remaining plaque remnants in some areas, and forming a rough surface. After CEA is completed, when it comes to the closure stage, it may be necessary to use a native or synthetic patch in some cases, as the lumen may narrow, while performing primary repair. The Cochrane database review focused on seven studies.[14] The results of 1,127 patients and 1,307 operations were examined, and the results of primary repair, vein grafts, and other grafts were analyzed. Although the data in the analyzed studies were insufficient and included methodological errors, the results obtained from the examined studies concluded that the risk of stroke was lower in the patch plasty group compared to the primary repair group, and arterial occlusion was lower in the patch plasty group in long-term follow-up. However, unlike retrospective analyses, randomized clinical studies revealed no statistically significant difference between these groups. Nevertheless, the evidence obtained is that the application of carotid patch plasty reduces the risk of occlusion and restenosis, as well as the combined stroke and mortality rate.[15] Considering the results of the materials used in patch plasty (Dacron®, polytetrafluoroethylene, or autologous), the difference between them was found to be small.[16,17] In our patient groups, there was no statistically significant difference in terms of the use of patches in either group. However, patches were not used in patients who developed mortality, morbidity, and late restenosis. In the eversion technique, when the ICA is completely transected from the bifurcation, the plaque is everted and removed from the ICA during CEA. Thus, no more tissue remains in the vessel wall, although problems may occur in reaching the proximal end point of the CCA and the distal end of the ECA. While the ICA is fully transected from the bifurcation, there is a possibility that adjacent nerves, particularly the Vagus nerve, can be damaged. In this method, the proximal mouth of the ICA is enlarged and sutured again to the bifurcation point

and, thus, it does not cause any surgical stenosis in the vessel lumen. In the Cochrane study, the eversion technique caused less restenosis than other techniques, the results obtained from other studies were similar, and no significant difference was observed in terms of neurological deficits between the eversion technique and classical CEA techniques.[18,19]

Although shunts are not used in the eversion technique, some surgeons have advocated the use of shunts, particularly in patients with an occluded contralateral carotid artery.[20] In the randomized International Carotid Stenting Study (ICSS) study, patients who underwent CAE and carotid stenting were applied diffusion-weighted magnetic resonance imaging to evaluate postoperative early (one to three days) acute ischemia, while fluid-attenuated inversion recovery investigation was conducted to evaluate late (four to six weeks) permanent brain damage.[21] Percentages of new ischemic events in the patients with early carotid stenting and in patients who underwent CAE were 46.4% and 14.1%, respectively. Most of the patients remained asymptomatic. In the late period, permanent cerebral abnormalities were detected to be 30% in the carotid stenting group and 8% in the CEA group.[22] Based on these results, it should be kept in mind that any further manipulation into the ICA may have more negative consequences than expected. In the European Carotid Surgery Trial (ECST) involving 1,729 patients, no statistically significantly positive results were found in terms of the use of shunts.[23] On the other hand, controlling the adequacy of cerebral perfusion with any non-invasive methods before deciding to use a shunt may prevent unnecessary usages. In the study of Ozer and Ceyran,[24] cerebral perfusion could be non-invasively determined using near infrared spectroscopy. Continuous measurement of cerebral oxygenation can be achieved by cerebral oximeter and more than 20% decrease compared to baseline levels shows a troublesome at cerebral perfusion. Conversely, preserved cerebral oxygen saturations after clamping carotid artery may give an insight that the adequacy of cerebral perfusion. Thus, unnecessary usage of shunts may be restricted.

In the MEE technique applied in our center, since, in an ideal plane, CEA was performed in the media adventitia junction and as a complete block (CCA, ECA and ICA complete), there were no cases such as thinning of the vessel wall and tissue debris in the wall. The time of procedure was not long, as the method was practical and no extra-intervention (such as plate fixation or shunt placement) was applied. Of note, in the MEE method, cross-clamp time was shorter than classical CEA, consistent with previous studies.[25]

The main limitations to the present study are its retrospective nature with a relatively small sample size, the lack of mid- and long-term follow-up data, and lack of routine intraoperative monitoring of cerebral perfusion.

In conclusion, CEA is the primary treatment option in the light of available data in advanced CAS. Different techniques are used in this treatment. In our clinic, classical CEA and MEE are successfully applied as carotid artery surgery. In our study, we found no statistically significant difference between the two methods in terms of intraoperative mortality, morbidity, and restenosis rates. Based on these results, we suggest that the MEE applied in our clinic is as effective as classical CEA. We believe that this method should be kept in mind as an alternative to the classical CEA technique.

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Comparison of transperitoneal and retroperitoneal approach for aortoiliac artery occlusive disease

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ABSTRACT

Objectives: This study aims to compare retroperitoneal and transperitoneal approaches in the surgical management of aortoiliac artery occlusive disease and evaluate the advantages and disadvantages of both techniques.

Patients and methods: Between January 2005 and May 2013, a total of 125 patients (116 males, 9 females; mean age 60.9 years; range, 24 to 79 years) with aortoiliac artery occlusive disease were retrospectively analyzed. The patients were classified according to the paramedian incision in the retroperitoneal (n=84) and midline incision in the transperitoneal (n=41) surgical techniques. All patients were examined pre- and postoperatively for the ankle-brachial index (ABI), laboratory blood tests, type of anesthesia, length of hospital and intensive care unit (ICU) stay, amount of blood transfusion oral intake starting time, revision, extra-revascularization need, comorbidities, and mortality.

Results: In the retroperitoneal technique, oral intake starting time ($p<0.001$), length of ICU ($p<0.001$) and hospital stay ($p<0.001$) were shorter, and the amount of blood transfusion ($p<0.007$) was lower, compared to the transperitoneal technique. The patients who underwent one-side revascularization in the retroperitoneal group had epidural anesthesia (n=10). There was no significant difference in the mortality, revision, and the need for extra revascularization rates between the groups.

Conclusion: Paramedian incision and retroperitoneal surgical technique in aortoiliac occlusive management is effective and safe and can be done for unilateral extremities under epidural anesthesia.

Keywords: Aortoiliac occlusive disease, median incision, paramedian incision, retroperitoneal technique, transperitoneal technique.

Atherosclerosis is a common disease all over the world and leads to different types of cardiovascular problems, being the most common cause of death.[1] Modern technology of pharmaceutical manufacturing, surgical equipment, and techniques have played a dramatic role in the treatment of such diseases; however, the morbidity and mortality rates are still high, mainly in less developed countries. Currently, different surgical approaches are used to treat this type of vascular disease. Earlier, transperitoneal approach with a midline incision was the most commonly used technique; however, later on, retroperitoneal surgical technique with a paramedian incision, endovascular intervention, and laparoscopic grafting techniques started to take place in the management.[2-4]

In recent years, laparoscopic aortobifemoral bypass grafting has been used in the management of aortofemoral artery occlusive disease as a minimally invasive surgical approach, although there is still no study directly comparing laparoscopic aortobifemoral bypass with endovascular treatment for extensive aortoiliac occlusive disease.[5,6] In the present study, we aimed to compare retroperitoneal and transperitoneal approaches in aortoiliac occlusive diseases and to evaluate the advantages and disadvantages of each technique.

PATIENTS AND METHODS

This retrospective study included a total of 125 patients (116 males, 9 females; mean age 60.9 years; range, 24 to 79 years) with aortoiliac artery occlusive disease between January 2005 and May 2013. Surgical interventions were performed in all patients according to the criteria of the

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Trans-Atlantic Inter-Society Consensus II (TASC-II)[7] and only the patients who had ischemic pain, ischemic ulcers, risk of losing extremity, and whose life quality was adversely affected underwent operation (TASC-II C or D).[7,8] A total of 84 patients were operated by a paramedian incision and retroperitoneal (Group 1), while 41 patients were operated with a midline and transperitoneal approach (Group 2). All patients were examined pre- and postoperatively for the ankle-brachial index (ABI), laboratory blood tests, type of anesthesia, length of hospital and intensive care unit (ICU) stay, amount of blood transfusion oral intake starting time, revision, extra-revascularization need, comorbidities, and mortality.

A written informed consent was obtained from each patient. The study protocol was approved by Pamukkale University, Faculty of Medicine, Ethics Committee (No. 366192). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Surgical technique

The decision of which surgical technique to be used was made based on the patient's general condition, his/her history of previous abdominal surgeries, and the surgeon's discretion. There were no strict criteria for the decision process.

General anesthesia was given to all patients, except for 10 who received epidural anesthesia according to the high risk or upon their request. They were all from the retroperitoneal group and operated for unilateral revascularization.

Retroperitoneal aortoiliac/aortobifemoral bypass with a paramedian incision:

A paramedian and vertical incision was done, in about 6 cm far from the midline and about 7 to 8 cm in length, starting few cm above the umbilicus downward to the suprapubic level (Figure 1). The anterior rectus sheet and, then, external abdominal muscle were opened at the external side, while the posterior rectus sheet was opened at its semilunar line. All abdominal wall layers were opened, except for the peritoneum (i.e., skin, subcutaneous tissue, superficial fascia, external, then, internal oblique muscle, transversus abdominis muscle, transversalis fascia, and preperitoneal adipose). After retroperitoneal space was reached, dissection was done toward the abdominal aorta and iliac arteries, and the contralateral iliac artery was reached retroperitoneally. In case of aortofemoral bypass, the femoral artery was reached via a tunnel retroperitoneally to the femoral region which was prepared priorly. The anastomosis was done in the same fashion.

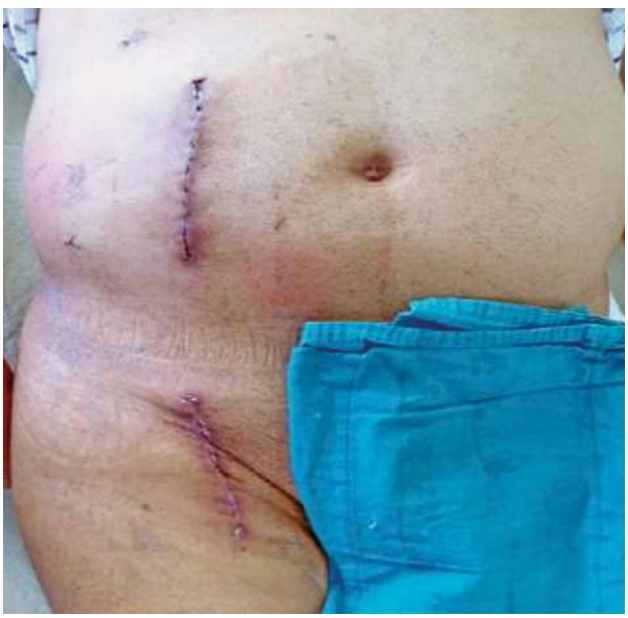

Figure 1. Right sided paramedian retroperitoneal laparotomy and right sided femoral incision for unilateral aortofemoral bypass grafting.

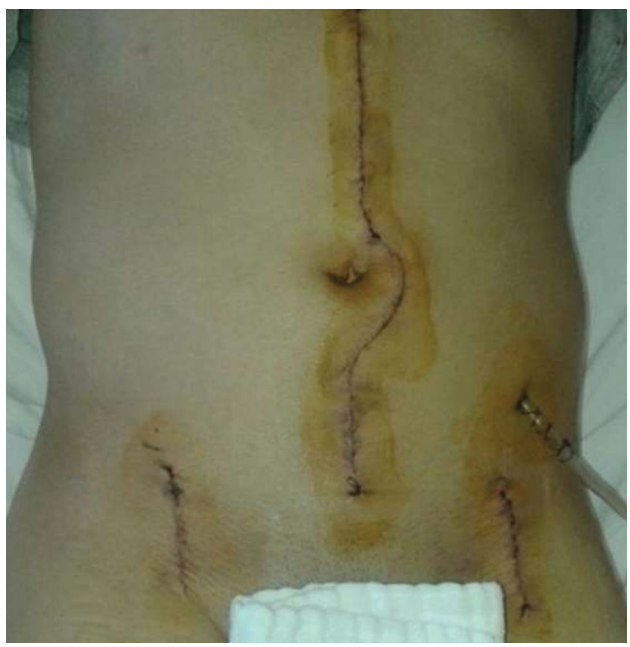

Figure 2. Midline transperitoneal laparotomy and bifemoral incisions for aortobifemoral bypass grafting.

Transperitoneal aortobiiliac/aortobifemoral bypass with a midline incision:

Laparotomy was done at the midline starting from the lower border of xiphoid bone toward the lower part of the umbilicus (Figure 2). The abdominal cavity was opened through the peritoneum. The left transverse colon was pulled upward, while the small intestine was pulled to the right side by sterile wet compresses. A gentle dissection and release were done to the abdominal aorta up to renal arteries and downward to the distal iliac arteries. Anticoagulant (heparin) was given at a dose of 1 mg/kg to maintain the activated clotting time (ACT) at 250 to 350 sec. Cross-clamping was applied at the proximal abdominal aorta below the renal arteries level. The 'Y' shaped Dacron® (JOTEC-Germany) grafts (16/8 mm) were used for aortoiliac or aortobifemoral replacements, while polytetrafluoroethylene grafts were used for femoropopliteal bypass grafting. Longitudinal arteriotomy was done to the aorta and end-to-side anastomosis was achieved by 3/0 or 4/0 polypropylene sutures. Then, cross-clamps were applied to the iliac arteries and released from the abdominal aorta. The legs of the graft were anastomosed to the iliac arteries in an end-to-side fashion by 5/0 polypropylene sutures. In aortobifemoral bypass grafting, the legs of the graft were anastomosed to the common femoral arteries which were exposed through the femoral region incisions priorly.

Table 1
Baseline demographic and clinical data of patients

	Surgical technique			
	Group 1 (n=84)	Group 2 (n=41)	Total (n=125)	
	n	n	n	*p*
Sex				0.269
Male	76	40	116	
Female	8	1	9	
Hypertension	32	16	48	0.920
Diabetes mellitus	24	10	34	0.620
Chronic renal failure	14	6	20	0.771
Cigarette	55	29	84	0.557
Chronic obstructive pulmonary disease	28	20	48	0.095
Hyperlipidemia	34	18	52	0.715
Revision	11	6	17	0.814
Mortality	4	0	4	0.302
Anesthesia				0.030
General anesthesia	74	41	115	
Epidural	10	0	10	
Revascularization type				<0.001
Aortofemoral	46	3	49	
Aortobifemoral	18	35	53	
Iliofemoral	18	0	18	
Aortoiliac	2	3	5	
Coronary artery disease				0.649
Coronary artery bypass grafting	10	6	16	
Medical treatment	28	17	45	
Stent	3	2	5	
Additional operation				0.081
Femoropopliteal	19	8	27	
Bilateral femoropopliteal	2	5	7	

Statistical analysis

Statistical analysis was performed using the PASW version 17.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed in mean and ± standard deviation (SD) or median (min-max), while categorical variables were expressed in number and frequency. The chi-square test was used to analyze categorical variables, while the Student t-test was used to analyze continuous variables between the groups. The repeated-measures t-test was performed to compare pre- and postoperative variables. A p value of <0.05 was considered statistically significant.

RESULTS

Only 10 patients in Group 1 were operated under epidural anesthesia, while the other 115 were operated under general anesthesia. Twenty-one patients from

Table 2
Pre- and postoperative data

	Surgical technique	n	Mean±SD	p
Age (year)	Group 1	84	61.2±9.7	0.597
	Group 2	41	60.3±9.5	
Intensive care unit (day)	Group 1	84	0.8±1.0	<0.001
	Group 2	41	2.0±1.3	
Hospitalization (day)	Group 1	84	6.9±4.1	<0.001
	Group 2	41	11.2±5.8	
Follow-up (month)	Group 1	80	24.3±11.1	0.841
	Group 2	41	24.7±9.6	
Glucose (mg/dL)	Group 1	84	121.8±48.2	0.372
	Group 2	41	130.5±56.1	
Preoperative Hb (gr/dL)	Group 1	84	13.3±1.6	0.508
	Group 2	41	13.1±1.8	
Postoperative Hb (gr/dL)	Group 1	84	11.1±1.4	0.180
	Group 2	41	13.5±16.3	
Preoperative Hct (%)	Group 1	84	39.4±4.5	0.649
	Group 2	41	39.0±5.4	
Postoperative Hct (%)	Group 1	84	36.3±32.4	0.503
	Group 2	41	32.9±2.8	
Preoperative creatinine (mg/dL)	Group 1	84	1.0±0.5	0.359
	Group 2	41	0.9±0.2	
Postoperative creatinine (mg/dL)	Group 1	84	1.2±0.9	0.423
	Group 2	41	1.0±0.4	
Preoperative ankle-brachial index	Group 1	84	0.5±0.1	0.537
	Group 2	41	0.5±0.1	
Postoperative ankle-brachial index	Group 1	84	1.0±0.1	0.071
	Group 2	41	0.9±0.2	
Oral intake (day)	Group 1	84	1.2±0.5	<0.001
	Group 2	41	1.8±0.8	
Blood transfusion (unit)	Group 1	84	1.3±1.8	0.007
	Group 2	41	2.3±2.1	

SD: Standard deviation; Hb: Hemoglobin; Hct: Hematocrit.

the retroperitoneal group needed an extra operation for peripheral arterial occlusive diseases such as femoropopliteal bypass grafting, while 11 patients needed to be taken to the operating room once again for exploration due to bleeding or early graft occlusion or distal thromboembolism.

The postoperative mortality was seen only in Group 1 (n=4). The main type of revascularization was aortofemoral bypass grafting, mainly in Group 1 (n=46), while a higher number of patients needed aortobifemoral bypass grafting in Group 2 (n=35). Iliofemoral bypass grafting was done only in Group 1 (n=18). Baseline demographic and clinical characteristic of the patients are summarized in Table 1.

The retroperitoneal approach with a paramedian incision showed superiority to the transperitoneal approach with a median incision in terms of the length of ICU stay (p<0.001) and hospital stay (p<0.001). The mean length of ICU stay was 0.78±1 days in Group 1 and 2.0±1.3 days in Group 2. The mean

Table 3
Pre- and postoperative data according to surgical incision in patients undergoing bilateral revascularization

	Surgical technique	n	Mean±SD	*p*
Age (year)	Paramedian incision	18	62.3±8.9	0.266
	Median incision	35	59.2±9.6	
Hospitalization (day)	Paramedian incision	18	5.39±1.6	<0.001
	Median incision	35	11.4±6.1	
Intensive care unit (day)	Paramedian incision	18	0.6±0.9	<0.001
	Median incision	35	2.1±1.4	
Blood transfusion (unit)	Paramedian incision	18	0.7±0.9	<0.001
	Median incision	35	2.4±2.2	
Preoperative Hb (gr/dL)	Paramedian incision	18	13.3±1.9	0.583
	Median incision	35	13.0±1.7	
Postoperative Hb (gr/dL)	Paramedian incision	18	11.4±1.7	0.557
	Median incision	35	13.9±17.6	
Preoperative Hct (%)	Paramedian incision	18	39.5±5.1	0.555
	Median incision	35	38.6±5.2	
Postoperative Hct (%)	Paramedian incision	18	33.5±4.2	0.467
	Median incision	35	32.7±2.5	
Glucose (mg/dL)	Paramedian incision	18	107.9±27.7	0.057
	Median incision	35	130.8±58.2	
Preoperative creatinine (mg/dL)	Paramedian incision	18	1.1±0.9	0.151
	Median incision	35	0.9±0.2	
Postoperative creatinine (mg/dL)	Paramedian incision	18	1.2±0.8	0.457
	Median incision	35	1.0±0.4	
Preoperative ankle-brachial index	Paramedian incision	18	0.5±0.1	0.301
	Median incision	35	0.5±0.1	
Postoperative ankle-brachial index	Paramedian incision	18	1.0±0.1	0.140
	Median incision	35	0.9±0.2	
Oral intake (day)	Paramedian incision	18	1.3±0.6	0.033
	Median incision	35	1.8±0.8	

SD: Standard deviation; Hb: Hemoglobin; Hct: Hematocrit.

length of hospital stay was 6.8±4.0 days in Group 1 and 11.1±5.8 days in Group 2. The mean oral intake starting time was earlier in Group 1 than Group 2 (1.2±0.5 days vs. 1.76±0.7 days, respectively; p<0.001). The mean amount of blood transfusion was also lower in Group 1 than Group 2 (1.26 U vs. 2.27 U, respectively; p<0.007) (Table 2).

Revascularization type and operations varied among the patients according to the occlusion site. Aortobifemoral bypass grafting were mostly done with a median incision and transperitoneal approach (n=35) and only 18 patients were operated for the same lesion type by the other technique. All iliofemoral bypass grafting procedures (n=18) were done with a paramedian retroperitoneal approach.

When the patients needed extra-revascularization operation for more distal lesions, the extra-grafting bypass operations were done in the same session. There were 19 patients from the retroperitoneal group and eight patients from the transperitoneal group who were operated with unilateral femoropopliteal grafting bypass, while two from the retroperitoneal group and five from the transperitoneal group were operated with bilateral femoropopliteal grafting bypass. Seventeen patients were taken to the operation room postoperatively for revision due to bleeding or early graft occlusion. Eight of them were operated before with a retroperitoneal approach and nine patients were operated with a transperitoneal approach. The reasons for revision was bleeding, mostly from the site of anastomosis.

Mortality was seen only in the retroperitoneal group where four patients (3%) died postoperatively, three of them were operated with a paramedian aortofemoral and one with aortobifemoral grafting bypass. The causes of mortality were severe pulmonary disease (n=2), myocardial infarction (n=1), and resistant metabolic acidosis (n=1). There was no statistically significant difference in the mortality rate between the two groups (p=0.302). In addition, there was no significant difference in the other measurements including laboratory testing (Hg p=0.180, Hct % p=0.503, creatinine p=0.423) and ABI (p=0.071) (Table 2).

In the subgroup analyses, the incision type and unilateral and bilateral revascularization methods were examined separately. In this study, patients who underwent unilateral revascularization with a paramedian incision were compared with those who underwent unilateral revascularization with a median incision. Accordingly, paramedian incision did not provide a significant superiority to the median incision in unilateral revascularization. On the other hand, after the comparison of the patients who underwent bilateral revascularization with a paramedian incision with those who underwent bilateral revascularization with a median incision, the length of ICU and hospital stay, starting time of oral food intake, and the amount of blood transfusion were found to be statistically significantly superior in favor of the retroperitoneal technique with a paramedian incision (Table 3).

DISCUSSION

Currently, cardiovascular diseases are the leading cause of death worldwide. Over the past two decades, the mortality from cardiovascular disease has decreased in developed countries, while it still high in less developed ones.[1,9] Recent technology has played a key role in the development of treatment modalities. In the past, aortoiliac occlusive artery disease was primarily treated by transperitoneal laparotomy with a midline incision using vascular grafts, while it can be treated nowadays using novel methods of endovascular intervention techniques or by a paramedian incision and retroperitoneal technique.

In our study, the male-to-female ratio was 12.9:1. The reason for this distinct prevalence difference compared to the literature data can be attributed to our small sample size. In addition, elderly women living in the conservative region where the study was conducted were usually not active and remained asymptomatic, and the number of health institutions in this region is high. Also, the peripheral arterial revascularization operations performed in external centers were not included in this study.

In the present study, two patient groups who underwent revascularization for aortoiliac occlusive diseases were evaluated. We compared the ABI, glucose, hemoglobin, hematocrit, and serum creatinine levels pre- and postoperatively. Comorbidities of the patients, the need for blood transfusion, the length of stay in ICU and hospital, starting time for oral intake, and follow-up periods were examined. Risk factors for morbidity were also assessed. As it is well known, atherosclerosis is one of the risk factors of peripheral arterial disease. Diseases caused by atherosclerosis such as myocardial infarction, stroke, aortic, and lower extremity vascular disease are the

most important causes of mortality and morbidity in developed countries. Risk factors such as the use of tobacco products, dyslipidemia, hypertension, and diabetes mellitus increase the risk of atherosclerosis, leading to a more complicated course of clinical conditions due to atherosclerosis.[10-12] In our study, we found no significant relationship between any variable and the surgical technique used. The main findings of this study are that the mean oral intake starting time and length of ICU ($p<0.001$) and hospital stay were shorter, and the amount of blood transfusion was lower in the retroperitoneal technique, compared to the transperitoneal technique.

In a study comparing retroperitoneal versus transperitoneal approach in revascularization of aortoiliac artery occlusive patients, Sicard et al.[13] reported similar results. The amount of intraoperative blood loss significantly increased ($p<0.001$) and the postoperative oral intake starting time was longer ($p<0.001$) in the transperitoneal technique, while the length of stay in the hospital was shorter ($p<0.02$) in retroperitoneal technique. Similar results were also reported in other studies,[14,15] consistent with our findings. In another study which was done by Kalko et al.,[16] similar results were reported. In this study, 153 patients were included and 85 of them were operated with a transperitoneal approach, while 68 with a retroperitoneal approach for aortoiliac artery occlusion. The mean oral intake starting time was also shorter in the retroperitoneal approach in this study ($p<0.001$).

In cases where aortoiliac occlusion is accompanied by femoropopliteal occlusion, it is a matter of debate whether revascularization should be done for both aortoiliac and femoropopliteal occlusions or it is enough to do it for aortoiliac occlusion alone. It has been supported in many publications that if the blood flow of a deep femoral artery (DFA) is sufficient, peripheral arterial revascularization is not required.[17] The cornerstone for peripheral arterial revascularization decision is the flow of DFA. Recently, hybrid interventions have also started to take place in the treatment of peripheral arterial occlusive diseases.[18] In a study conducted by Madiba et al.,[19] 984 lower extremities of 492 patients were evaluated. All patients underwent aortobifemoral graft bypass operation due to aortoiliac artery occlusion disease. A total of 123 extremities of the superficial femoral artery were found to be patent, while it was occluded in 861 extremities. The effect of the patent DFA as runoff was investigated. Five-year patency rate was 80% in the extremities with the occluded superficial femoral artery and 87% in the extremities with the patent superficial femoral arteries. The main finding of this study is that, when DFA is patent the development of collateral arteries to the popliteotibial artery is high so, there is no need for distal revascularization.[19]

In our study, additional interventions were applied only to the patients with advanced peripheral arterial disease. Intermittent claudication alone was not considered as an indication for distal revascularization. In our clinic, in case of aortoiliac occlusive disease associated with peripheral arterial occlusions, the decision to perform extra-revascularization to the peripheral vessels depends on the flow of the DFA and whether there are signs of acute ischemia or non-healing ischemic wounds distally. Considering the possible relationship between reoperation and surgical technique, no significant difference was found between the techniques used in this study.

Furthermore, there was no significant difference in the follow-up duration between the two techniques. The prolonged follow-up was mainly due to the causes of acute circulatory disorders (i.e., thromboembolism) or to the situations in which complete revascularization was not achieved in the first operation. In our study, mortality was seen only in Group 1 ($n=4$, 3%), indicating no statistically significant difference. This may be related to the number of patients in each group.

Considering the difficulties of the surgical techniques, the surgical field was limited in Group 1 compared to Group 2. In general, there was a need for one more assistant specialist in Group 1 to help in retracting the nearby organs and tissues to achieve a better surgical field for the primary surgeon. In aortobifemoral or aortobiiliac operations, extending the femoral/iliac graft to the contralateral side was difficult, as well. At the same time, it is safer with less possibility of intestinal injury.[20] In Group 2, there were difficulties in operating abdomens with adhesions due to previous surgeries or inflammatory processes, resulting in incisional hernia, evisceration, peritonitis, and long-lasting ileus.[21]

The main limitation to this study is that the number of transperitoneal group patients may have affected the study results. The retrospective nature of the study is also another limitation. Further large-scale, long-term, prospective studies are needed to confirm these results.

In conclusion, retroperitoneal approach with a paramedian incision in treating aortoiliac artery occlusive disease seems to be superior to the transperitoneal approach with a median incision with less blood transfusion, shorter ICU and hospital stay, and earlier start of oral intake.

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Cardiovascular Surgery and Interventions

Case Report Open Access

An interarterial course of the left coronary artery: Pulmonary artery translocation procedure

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ABSTRACT

Congenital anomalies of the coronary arteries are rare congenital cardiac pathologies, representing 0.3 to 1.6% of congenital cardiac anomalies and are often associated with the cause of sudden death in the young individuals. Coronary artery anomalies consist of a wide range of abnormalities, including anomalous origin, anomalous course or both. In this report, we present a pediatric case of anomalous origin of the left main coronary artery from the right cusp with an interarterial course between the aorta and pulmonary artery.

Keywords: Coronary vessel anomalies, operative, sudden cardiac arrest, surgical procedures.

Congenital coronary artery anomalies are rarely seen. They are can be divided into subgroups based on anomalous origin, course, size, and numbers.[1] The term of the course of anomalous coronary artery refers to the fact that the coronary artery originates from another coronary sinus and runs along an alternative course to reach its region. The incidence of interarterial course of the left coronary artery is estimated at about 1.3% of coronary anomalies and is the most feared situation.[1,2] An aberrant left coronary artery with an interarterial course is a complex and malignant variant of coronary artery anomalies.

In this article, we present a pediatric case with anomalous origin and course of the left coronary artery, in which surgical correction with lateral translocation of the pulmonary trunk to the left pulmonary artery (PA) was performed successfully.

CASE REPORT

A 13-year-old male patient was referred to our department with chest pain. His medical history revealed that the chest pain was exacerbated by exercise and disappeared with rest. On physical examination, the vital signs were normal. Blood tests, electrocardiography, and chest X-ray findings were normal. The left coronary artery was unable to be visualized by transthoracic echocardiography in its usual location. Therefore, computed tomography (CT) examination was decided. Contrast-enhanced CT revealed that the left main coronary artery (LMCA) originated from the right coronary sinus (Figure 1). The right coronary sinus had only one ostium in the aortic sinus and the LMCA separated from the right coronary artery and was running posteriorly between the aorta and PAs (Figure 2). After the artery reached the posterior via the interarterial course, it divided into the left anterior descending artery and circumflex artery. The right coronary artery was originating from the aorta into the atrioventricular groove as usual. The patient's condition was discussed with pediatric cardiology and surgery was decided as the most optimal treatment option. A written informed consent was obtained from each parent.

During surgery, the mediastinum was approached via median sternotomy. The pericardium was incised and an aorto-bicaval cannulation was performed. Cardiopulmonary bypass was initiated and antegrade blood cardioplegia was infused for diastolic arrest.

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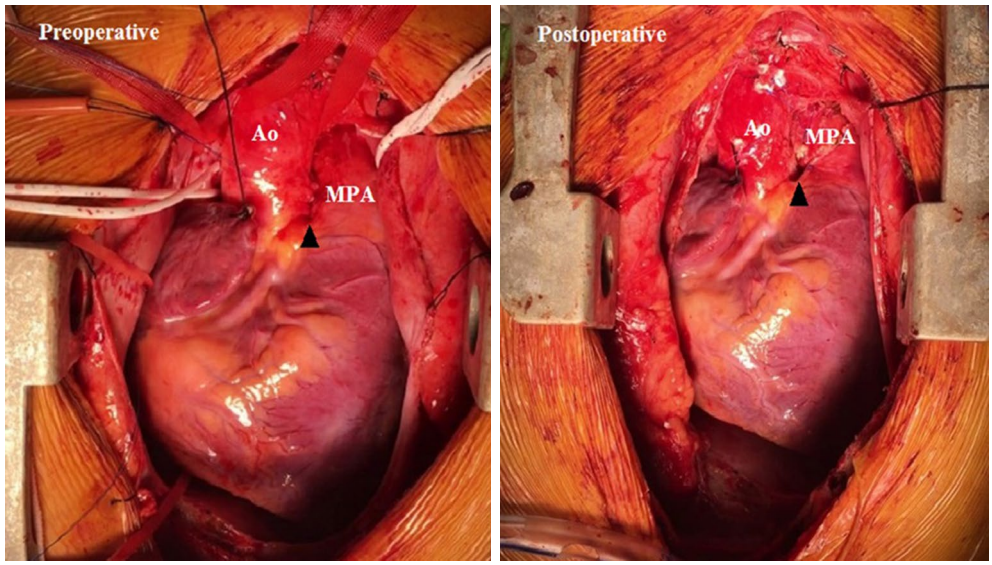

Figure 1. Three-dimensional computed tomography images. An anomalous origin of left main coronary artery arising from right cusp in a malignant configuration and course between aorta and pulmonary trunk.

Ao: Aorta; MPA: Main pulmonary artery.

Following diastolic arrest, the interarterial segment between the aortic root and main PA was dissected out carefully to avoid damage to the coronary artery and branches. The main PA was transected prior to pulmonary bifurcation. The gap at the pulmonary confluence was repaired using a pericardial patch. An incision was made on the left PA and the main PA was anastomosed to this incision. Following completion of the anastomosis, the space between aorta and PA increased (Figure 2). The cross-clamp time was 35 min. Total bypass time was 55 min. Following decannulation, the chest was closed in a routine fashion. The patient underwent successful surgical ventricular septal defect closure and reimplantation of the main PA to the left PA. Postoperative echocardiography demonstrated normal flow to the left PA. The patient recovered gradually without any complication. On the fifth postoperative day, he was eventually discharged.

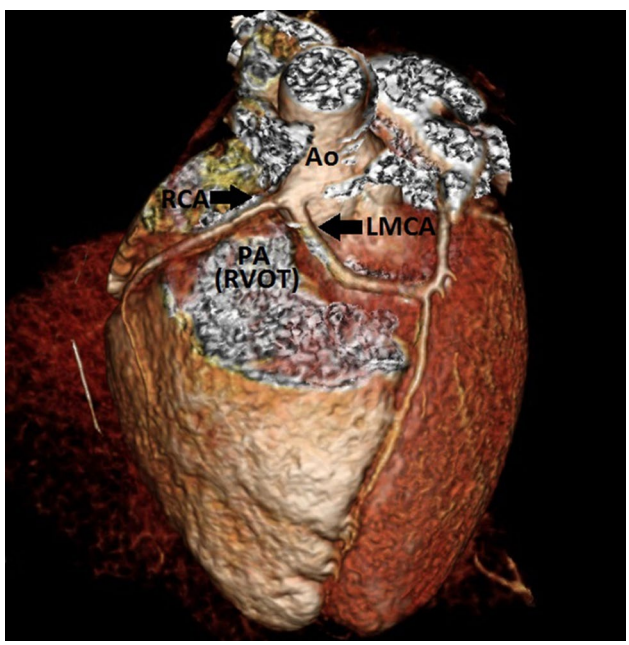

Figure 2. Intraoperative view. Division of main pulmonary artery with reanastomosis to left pulmonary artery. Note the increased distance between pulmonary artery and aorta (black arrows).

Ao: Aorta; LMCA: Left main coronary artery; PA: Pulmonary artery; RVOT: Right ventricular outflow tract; RCA: Right coronary artery.

DISCUSSION

Coronary artery anomalies are a rare group of congenital disease with an anomalous origin and course of the native coronary artery.[3,4] This course may be prepulmonic, subpulmonic, retroaortic, retrocardiac, or interarterial.[2] All courses with the exception of interarterial are considered benign. An interarterial course can lead to sudden cardiac arrest. Sudden cardiac death due to this anatomical entity is the

leading second cause of mortality in young competitive athletes on the playing field.[4-6]

The true incidence of this anomaly remains unknown due to the fact sudden cardiac arrest often represents as the initial symptom.[4] Early presymptomatic diagnosis presents as a serious challenge. This issue is the major drawback of the diagnosis before a cardiac event.[2] However, the minority of patients may refer to a consultant about non-specific chest pain, syncope, and arrhythmia.

An understanding of the anatomy of the coronary artery is required for optimal imaging. Transthoracic echocardiography is a non-invasive, effective, and first-line diagnostic tool.[3] However, echocardiography is operator-dependent, and image quality can vary depending on the operator's experience and the patient's acoustic window. On routine echocardiographic exam, certain markers of the anomaly may be present. These include a fail to see the coronary ostium in a routine fashion, unusual coronary ostia, and coronary artery images at unexpected areas. In these cases, further evaluation is needed. Although some cardiologists can diagnose the abnormal coronary pattern, it is not recommended to plan surgery solely based on with this examination.[3] In case of echocardiographic diagnosis or suspected existence, further evaluation is needed. Computed tomography angiography is the most appropriate imaging study for this indication which is considered as Class 1 indication.[4]

Surgical indication is in accordance with the most accepted expert consensus on surgical treatment.[4] The optimal management and surgical decision making for patients with coronary artery anomaly depend on multiple factors such type of coronary artery anomaly, age, and symptoms.[6] The key factor in the surgical procedure selection is detailed anomalous coronary artery anatomy. The important points on coronary artery anatomy include aortic sinuses and coronary ostia, intramural course, and acute angles.[5] Patients with LMCA and interarterial course should be treated surgically, even if there are no symptoms.[4] In our case, the coronary artery anatomy was negative for intramural course and acute angulations.

Although the most optimal surgical approach is still controversial, current surgical options include unroofing procedure, button detachment and reattachment procedure, coronary artery bypass grafting, and PA translocation.[4-6] Surgical planning should be performed based on the coronary artery anatomy. In our case, no intramural anatomy was observed and, therefore, the unroofing procedure was unnecessary. Additionally, there was no left main coronary ostium and, thus, the coronary button detachment and reattachment procedure was abandoned. There was another unfavorable option; coronary artery bypass grafting.[4,6] The reason why the bypass procedure is not favorable is the competitive flow due to anastomosis, iatrogenic injury to non-atherosclerotic, and stenosis-free artery via anastomosis.[5,6] The last procedure was PA translocation,[5] as it was thought to be the most appropriate option for our patient depending on his coronary artery anatomy. The PA lateral translocation procedure widens the gap between PA and aorta. Coronary artery compression is relieved via this maneuver. In our case, the surgical team decided performing PA lateral translocation procedure as the most optimal treatment option.

In conclusion, favorable surgical outcomes can be achieved with the appropriate method of surgical treatment of anomalies of the left coronary artery. As in our case, the lateral translocation procedure allows an anatomical reconstruction and is technically feasible as an effective surgical approach for patients with a suitable anatomy.

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Cardiovascular Surgery and Interventions

Case Report Open Access

Agenesis of the inferior vena cava: A rare cause of recurrent venous thromboembolism

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ABSTRACT

Agenesis of the inferior vena cava is a rare malformation. Inferior vena cava anomalies should be considered in the presence of recurrent thromboembolism or bilateral thromboembolism, particularly in young and middle-aged adults without any risk factors and family history. Herein, we present a case of agenesis of the inferior vena cava leading to recurrent venous thromboembolism in a middle-aged adult.

Keywords: Agenesis of inferior vena cava, thromboembolism, thrombosis.

Inferior vena cava (IVC) anomalies are extremely rare causes of deep vein thrombosis (DVT). The etiology of DVT must be specified, particularly in young patients. Young patients having bilateral DVT with no risk factor or family history are more likely to have IVC anomalies.[1] Also, IVC anomalies may be asymptomatic and incidentally diagnosed with abdominal imaging methods. The diagnosis of IVC anomalies is important to prevent new thromboembolic events. In particular, in young patients, DVT should be taken into consideration as a rare complication of IVC.

Herein, we present a case of inferior vena cava agenesis (IVCA) leading to recurrent venous thromboembolism in a middle-aged adult patient.

CASE REPORT

A 47-year-old male patient was admitted to our outpatient clinic with abdominal pain and regurgitation. The patient had a history of recurrent bilateral lower extremity DVT since the age of 20 years and pulmonary embolism four years ago. He was on rivaroxaban treatment for eight months. Physical examination revealed that the patient had dilated varicose veins and edema in the bilateral lower extremities (Figure 1). There was no history of thrombosis in the family. In the laboratory examination, the following results were obtained:

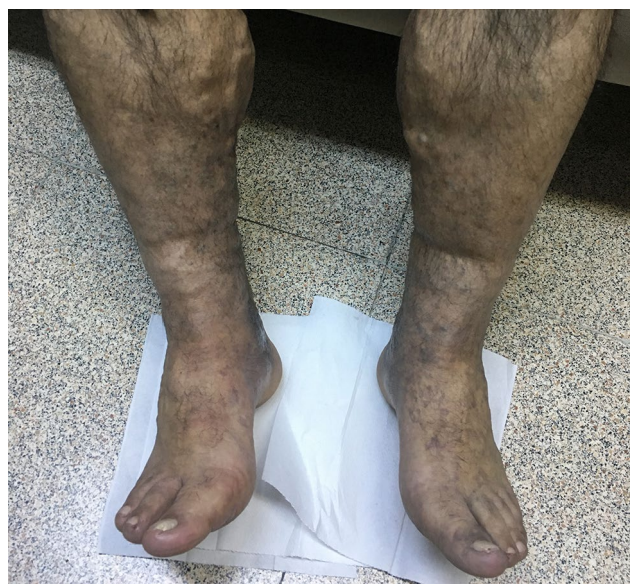

Figure 1. The patient had dilated varicose veins and edema in bilateral lower extremities.

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white blood cells count 5.03×10^3 cells/μL; hemoglobin 13.8 g/dL; platelets 203×10^3/L; C-reactive protein 1 mg/L; amylase 106 U/L, and lipase 118.1 U/L. The thrombophilia blood panel was studied in the laboratory, and no pathology was found to cause any prothrombotic tendency (Factor II, Factor V Leiden, Factor XIII, PAI, MTHFR C677T and MTHFR A1298C). On previous Doppler ultrasonography of the lower extremity performed four months ago, there were wall irregularities secondary to lower extremity thrombus in the bilateral superficial and popliteal vein. A chronic thrombus was detected in a short segment of the tibial and popliteal vein. Abdominal ultrasonography, which was performed due to abdominal pain, revealed an adenoma of 20-mm in diameter having a well-circumscribed margin on the right adrenal gland; and it was reported to be a suspicious lesion. Therefore, the patient underwent contrast-enhanced abdominal computed tomography (CT) scan, and numerous enlarged venous varicose veins were revealed in the paraaortic and paracaval space, presenting more prominently near the kidney on the left side (Figure 2a, b). Enlarged venous varicose structures

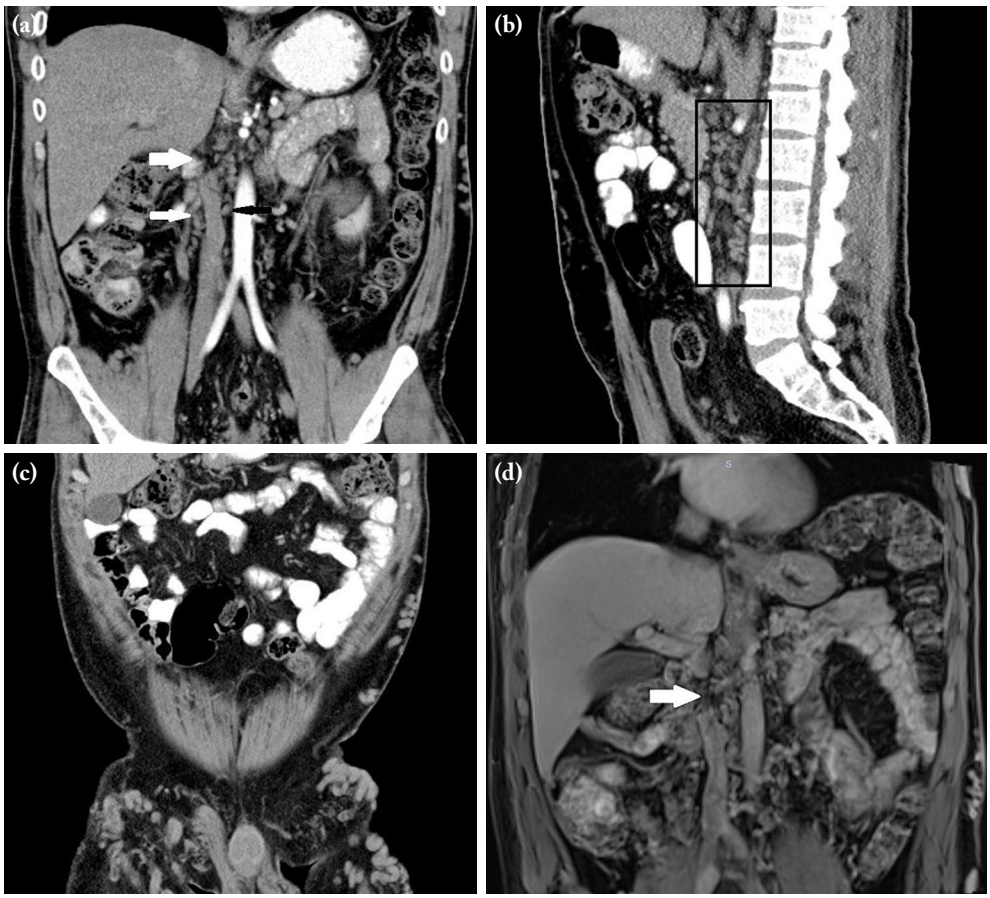

Figure 2. **(a)** In the coronal cross-sectional contrast-enhanced abdominal CT, the segment of inferior vena cava adjacent to lower contour of liver was not observed (thick arrow). On both sides of this segment, there were dilated and tortuous venous structures compatible with collateral vessels (thin arrows). **(b)** In the sagittal cross-sectional contrast-enhanced abdominal CT, prevertebral and retroperitoneal collateral dilated venous structures were observed. **(c)** In the coronal cross-sectional contrast-enhanced abdominal CT, numerous dilated and tortoise veins were observed under skin in both inguinal regions and anterior wall of abdomen on the left. **(d)** In the post-contrast late phase T1-weighted MR images, the segment of inferior vena cava adjacent to lower contour of liver was not observed.

CT: Computed tomography; MR: Magnetic resonance.

were observed within the subcutaneous fat tissue of the anterior wall of the left abdomen and bilateral inguinal region (Figure 2c). The patient underwent abdominal magnetic resonance imaging and multiple venous collateralizations at the splenic hilum and left perirenal space, left renal hilum and left paraaortic and right paracaval region and segmental IVCA was observed (Figure 2d). The diameter of the IVC was found to be remarkably reduced. The relationship between the vena cava and left renal vein at the midline of the abdomen was consistent with the retrocaval renal vein, the changes related to IVCA, and collateral vessels. The diameter of the distal iliac veins was also found to be considerably reduced, particularly on the left side, and the left iliac vein was hypoplasic. It was evaluated as the segmental congenital IVCA. Thus, multidisciplinary evaluation was performed, and it was decided to monitor the patient with anticoagulant therapy without any surgical planning. A written informed consent was obtained from the patient.

DISCUSSION

The congenital IVCA is rare. It usually presents with idiopathic DVT of the lower extremity.[1,2] In general population, the overall incidence of congenital IVCA is estimated to be 0.0005 to 1%; however, it is found in 5% of patients with idiopathic DVT aged <30 years.[3]

The IVC develops between the sixth and eighth weeks of the embryonic life and contains three pairs of embryonic vein anastomosis, which are posterior cardinal veins, sub-cardinal veins, and supra-cardinal veins.[4] A normal IVC transforms into a one-sided system on the right, comprising hepatic, prerenal, renal, and postrenal segments.[5] As a result of the lack of this development during embryogenesis, IVC anomalies occur. Due to differences in this embryonic development, different types of IVC anomalies may occur. The IVC anomalies are seen nearly 0.5% of general population.[3] Duplicated IVC and left IVC are the most common IVC anomalies.[6] The IVCA is a rare variant and can be full or segmental. These anomalies may be associated with non-specific symptoms or completely asymptomatic, and the diagnosis is usually made incidentally during imaging studies.[7]

Insufficiency in collateral circulation in the IVC anomalies causes venous stasis and thromboembolic events.[5,8] Although susceptibility to thromboembolism in IVCA is a well-defined entity, there is no gold standard treatment regimen. Oral anticoagulants are often used in the treatment.[9]

In appropriate cases, thrombolysis is combined.[7] Since IVC anomalies are associated with recurrent thromboembolism, patients should be informed that they should not remain immobile for long periods of time and they should refrain from oral contraceptive use.[10] Ultrasonography is often insufficient to detect IVC anomalies. Contrast-enhanced CT and magnetic resonance angiography should be used in the diagnosis.[11]

In conclusion, inferior vena cava anomalies should be considered in young and middle-aged patients with thromboembolism who do not have any risk factors or family history. As these patients may seek medical advice due to recurrent thromboembolic episodes, they can be treated with long-lasting anticoagulants. A close clinical follow-up is required for recurrent episodes and to observe the side effects of anticoagulant therapy. Therefore, it is of utmost importance to identify these patients using imaging studies to determine the etiology of the disease.

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Cardiovascular Surgery and Interventions

Case Report Open Access

A rare problem in a pregnant woman with COVID-19 pneumonia: Pneumomediastinum and subcutaneous emphysema

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ABSTRACT

Novel coronavirus disease-2019 (COVID-19) has affected millions of individuals within in a short period of time, resulting in hundreds of thousands of deaths, and has led to a crisis worldwide. A 22-year-old pregnant woman (32 weeks of gestation) was admitted to our clinic with a suspicion of COVID-19. Initially, radiological evaluation using computed tomography (CT) imaging was unable to be performed, as the patient refused imaging study; however, we were able to obtain CT following emergency cesarean section. On CT scan, pulmonary lesions were predominant at the lower zones and progressed to confluent bilateral consolidation with pneumomediastinum, confirming COVID-19 pneumonia and pneumomediastinum complications. In conclusion, although rare, spontaneous pneumomediastinum should be considered in COVID-19 infection.

Keywords: Complication, computed tomography, coronavirus, COVID-19, pneumomediastinum, pneumonia, pregnant woman.

Pneumomediastinum is classified as primary (spontaneous) or secondary pneumomediastinum.[1,2] There is no obvious underlying cause in spontaneous mediastinum, while there is an apparent cause such as trauma, intra-thoracic infection, and injuries of respiratory or gastrointestinal tracts in the secondary type. Majority of cases develop due to traumatic causes.[1,2] Although spontaneous pneumomediastinum is rare, it is often seen in healthy, young men as a result of rupture of the peripheral pulmonary alveoli.[1,2] Other potential causes include barotrauma during mechanical ventilation, hyperbaric therapy, elevation phase of diving, asthma or obstructive airway, such as foreign body aspiration. In addition, pneumomediastinum has been also reported following tooth extraction, tonsillectomy, tracheostomy, head and neck surgery, and craniofacial trauma.[1,2]

In late December 2019, several pneumonia cases with an unknown etiology were reported from Wuhan Province of China and evolved to global pandemics. The causative agent was initially designated as acute respiratory distress syndrome-coronavirus-2 (SARS-CoV-2); subsequently, it was denoted as novel coronavirus disease-2019 by the World Health Organization (WHO).[3,4] Pulmonary parenchymal opacities are frequently seen on chest radiographs. Complications of severe COVID-19 pneumonia were reported in few cases.[5]

In this article, we report a young pregnant woman with pneumomediastinum as a potential, rare complication of COVID-19 pneumonia.

CASE REPORT

A 22-year-old pregnant woman (32 weeks of gestation) without a known systemic disease was admitted to our clinic with fever. The patient refused computed tomography (CT) imaging due to potential harms of CT during pregnancy. She had no respiratory, circulatory, or metabolic problem requiring intensive care unit (ICU) admission and was admitted to the pandemic clinic with suspected COVID-19. As the polymerase chain reaction (PCR) test was positive, a loading dose of hydroxychloroquine 400 mg b.i.d.,

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followed by a maintenance dose of 200 mg b.i.d. and a loading dose of azithromycin 500 mg b.i.d., followed by a maintenance dose of 250 mg b.i.d. were prescribed based on the COVID-19 National Treatment Guidelines. On Day 3 after admission, the patient had hypoxemia (peripheral oxygen saturation [sPO_2]: 80%) and tachypnea (respiration rate: 36/min); thus, she was admitted to the pandemic ICU.

In the first assessment in the ICU, the patient had dyspnea, severe tachypnea (respiration rate: 36/min) and tachycardia (heart rate: 130 bpm). The sPO_2 value was 78% under oxygen supplementation (6 to 8 L/min) via the face mask. Non-invasive mechanical ventilation was initiated (via full-face mask; pressure-assisted ventilation mode; positive end expiratory pressure [PEEP]: 7 cmH_2O and pressure support [PS]: 14 cmH_2O; 50% oxygen supplementation). The sPO_2 value was improved to 97% and tachypnea was decreased (respiration rate: 24/min). After ICU admission, high-flow nasal oxygen supplementation (37°C; 60 L/min flow and 40% oxygen) and interrupted non-invasive mechanical ventilation (50% oxygen; PEEP: 7 cmH_2O; PS: 14 cmH_2O; pressure-assisted ventilation mode, via an oronasal mask) were applied until Day 9.

On Day 4 after the ICU admission, new-onset chest pain developed. Subcutaneous emphysema was palpated on the upper one-third of left thoracic wall, particularly over the clavicle. Chest auscultation findings were normal. The radiological chest imaging was planned to the patient; however, the patient refused any type of imaging study. Thus, lung sonography was planned to the patient. However, due to the settings of COVID-19 ICU and unfavorable general health status of the patient, an adequate assessment could not be performed. As there was no alteration in clinical findings, hypoxemia level and ventilation parameters, we continued to follow the patient with the available status.

The patient was maintained by alternate ventilation strategy (5-h high-flow nasal oxygen followed by 1-h non-invasive mechanical ventilation; however, on Day 7, the need for non-invasive mechanical ventilation increased due to hypoxemia with a sPO_2 of 85 to 90 cmH_2O); thus, a sonography was performed by an obstetrician, revealing the decreased amnion fluid. An emergency cesarean section was performed

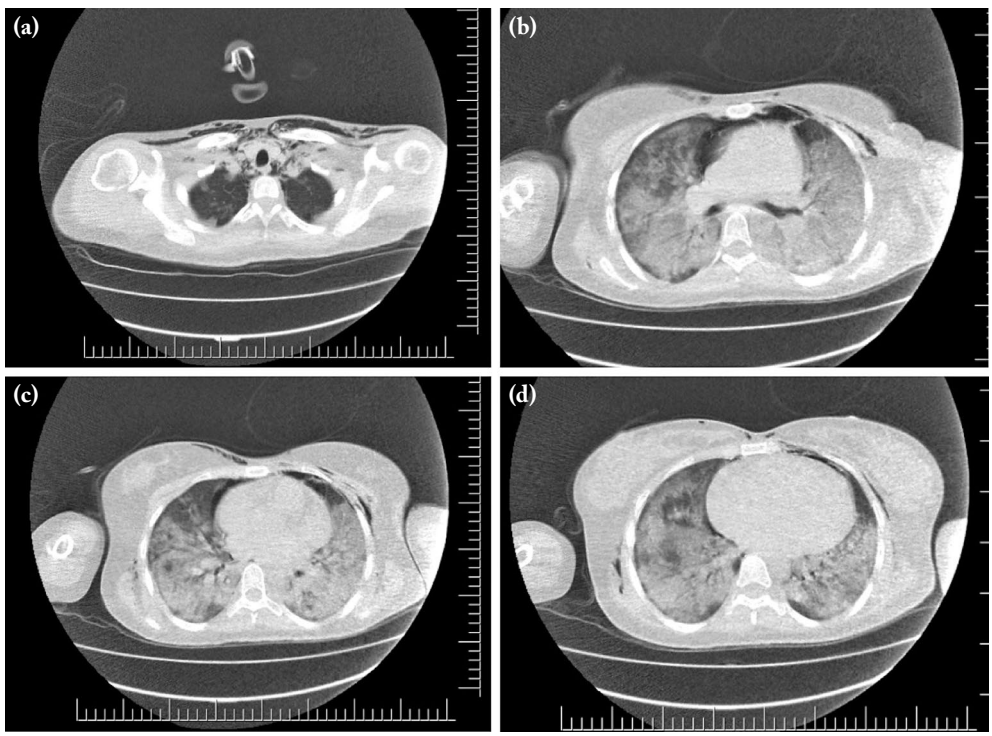

Figure 1. Initial computed tomography scans after cesarean section. **(a)** Subcutaneous emphysema; **(b-d)** pneumomediastinum and bilateral ground-glass opacities.

under spinal due to the decreased amnion fluid and profound hypoxemia anesthesia in the patient on non-invasive mechanical ventilation. Two PCR tests with a 24-h interval were negative for COVID-19 in the infant; thus, newborn was discharged after seven days of ICU admission.

The CT imaging which was refused initially by the patient was performed after cesarean section and revealed multiple diffuse patchy consolidation areas and ground-glass opacities in both lungs and pneumomediastinum, confirming COVID-19 pneumonia, pneumomediastinum without pneumothorax and subcutaneous emphysema (Figure 1a-d). As pneumothorax was lacking and pneumomediastinum caused no compression, no surgery was planned. On Day 2 after cesarean section, orotracheal intubation was performed and mechanical ventilation was initiated due to worsening in the general health status and respiratory parameters on Day 9 after admission. The following parameters were used for ventilation: pressure-regulated volume control mode; tidal volume, 550 mL, frequency, 16/min, PEEP: 10 cmH_2O and FiO_2: 80%.

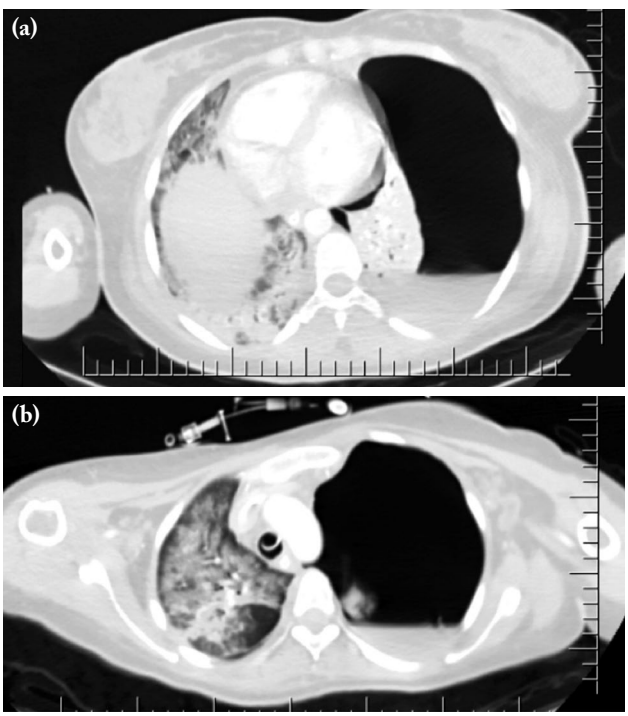

Figure 2. Control computed tomography scans showing no pneumomediastinum. **(a)** Massive pneumothorax and pleural effusion at left; **(b)** right-sided cardiac shift and massive pneumothorax at left.

Due to worsened gas exchange (P/F:70), the patient was placed to the prolonged prone position (22 h). On Day 14 after detection of pneumomediastinum on the first CT scan, a control CT imaging was performed in the patient who had deterioration in gas exchange, respiratory parameters, and hemodynamics and revealed massive pneumothorax in the left lung and disappearance of previous subcutaneous emphysema (Figure 2a, b). Thus, a chest tube was inserted via thoracostomy from the left side. During follow-up, *Acinetobacter baumannii* sepsis, deep venous thrombosis in the left femoral vein, and subsequent pulmonary embolism developed. The patient died on Day 22 after the ICU admission, despite all efforts.

DISCUSSION

Pneumomediastinum is a rare entity. In previous studies, the pneumomediastinum incidence has been reported as 1:800 to 1:42,000 in children presented to emergency department and 1:15,500 admissions in general population. The mean age at onset is 19 years.[1,2] The pain is the most common presenting symptom in 80 to 90% of patients.[1,2] In our case, similarly, the first complaint in the ICU was chest pain.

Computed tomography plays a major role in the diagnosis of COVID-19 pneumonia, which is an ongoing global problem. Although many parenchymal or non-parenchymal findings are seen on CT scans, the most common finding is ground-glass opacities in parenchyma.[6] Spontaneous pneumomediastinum is an extremely rare condition. The most common clinical findings include fever, cough, myalgia, or fatigue.[6] Our patient refused radiological evaluation due to potential harms of CT during pregnancy; thus, the diagnosis was made based on PCR testing and clinical presentation, and no radiological examination was able to be performed initially. Such findings should be addressed meticulously, particularly in the course of COVID-19 pneumonia. Thus, diagnosis through early imaging studies and timely treatment of COVID-19 complications can improve therapeutic effectiveness and decrease mortality.[5]

Pneumothorax and pneumomediastinum have been rarely reported in COVID-19 pneumonia. The pneumomediastinum was not only observed without parenchymal lesion,[7] but also observed with ground-glass opacities, findings of pneumonia, and pulmonary parenchymal injury.[5,8] In our patient, pneumomediastinum was present with findings

of COVID-19 pneumonia. In previous reports, there was no comorbid condition such as asthma or chronic lung disease which may contribute to available condition or invasive interventions leading to iatrogenic pneumothorax; therefore, all previous cases were considered COVID-19-related spontaneous pneumomediastinum.[5,7,8] Although pregnancy, itself, has been reported as a cause of spontaneous mediastinum,[1,2] we believe that severe, dry cough, and pulmonary injury caused by COVID-19 could be the cause of pneumomediastinum. Although severe pulmonary injury was seen in on the initial thoracic CT scan, it was thought that pneumomediastinum without pneumothorax was surprising.

During pandemic, four pregnant women were treated in our hospital. All patients were treated in accordance with the COVID-19 National Treatment Guidelines. Of these patients, three women were discharged successfully; however, the present case died.

In conclusion, although spontaneous pneumomediastinum is rarely seen in COVID-19 infection, it can develop due to severe cough and respiratory distress. Spontaneous pneumomediastinum is usually a self-limiting disorder, although the exact mechanism is still unknown. However, it has potential to cause severe circulatory or respiratory disorder. Thus, spontaneous pneumomediastinum in COVID-19 patients should be closely monitored as a potential marker for progression.

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Cardiovascular Surgery and Interventions

Case Report Open Access

Septal myectomy and chordae repair in hypertrophic obstructive cardiomyopathy: A case report

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ABSTRACT

Hypertrophic obstructive cardiomyopathy is a cardiac disease presenting with the thickened heart muscle and may obstruct left ventricle outflow. A 32-year-old male patient was admitted to our clinic with complaints of weakness, fatigue, and abdominal pain, mostly after meals. He had a systolic anterior motion of the mitral valve concomitantly. He was operated with septal wedge myectomy, resection of the secondary chordae, and plication of the anterior leaflet via the aortic orifice. In conclusion, in such cases the results are satisfactory; however, some patients may later develop mitral regurgitation over time.

Keywords: Chordae repair, hypertrophic obstructive cardiomyopathy, septal myectomy, systolic anterior motion of the mitral valve.

Hypertrophic cardiomyopathy is an inherited disease and occurs in about 1/500 of the population.[1] When left ventricle outflow tract (LVOT) obstruction occurs, the most optimal treatment is surgical septal myectomy. When the gradient at the level of the LVOT obstruction is ≥50 mmHg at rest and the patient is considered in the New York Heart Association (NYHA) Class III-IV, surgical septal myectomy is recommended.[2]

In this article, we present a case of a hypertrophic septum with the systolic anterior motion (SAM) of the mitral valve successfully treated with aortotomy, wedge resection of the interventricular septum, mitral valve repair.

CASE REPORT

A 32-year-old male patient presented to our clinic complaining of weakness, fatigue, and abdominal pain, mostly after meals. Investigations were done and the echocardiography showed a mild (2nd degree) eccentric mitral valve failure with a SAM of the mitral valve, associated with a thickened septum and diagnosed as a case of hypertrophic obstructive cardiomyopathy (HOCM). The LVOT gradient was 162/85 mmHg. Mitral valve replacement was recommended to the patient; however, he insistently requested mitral valve repair. A written informed consent was obtained from the patient.

Preparations for the operation were made and the patient underwent an operation where the aortic two-stage venous cannulation was done. After giving a cardioplegic solution in the fashion of antegrade and retrograde, cardiac arrest was achieved and, then, aortotomy was done. Exploration of the septum and mitral valve was done via the aortic orifice. The septum was found to be thickened. Anterior chordae were elongated, leading to SAM of the mitral valve (Figure 1). Septal myectomy was done by resecting a piece of about 8 mm from the septum, while the anterior leaflet was plicated by 6.0 polypropylene suture through the aortic valve. The suture line was along the clear zone of the mitral anterior leaflet. We resected the secondary chordae that tightened the anterior leaflet. Intraoperative transesophageal echocardiography was used to evaluate valves, SAM of the mitral valve, and LVOT gradient. There were no severe LVOT gradient. The mitral valve was perfectly coaptating and no SAM or mild degree regurgitation was found in the mitral leaflet.

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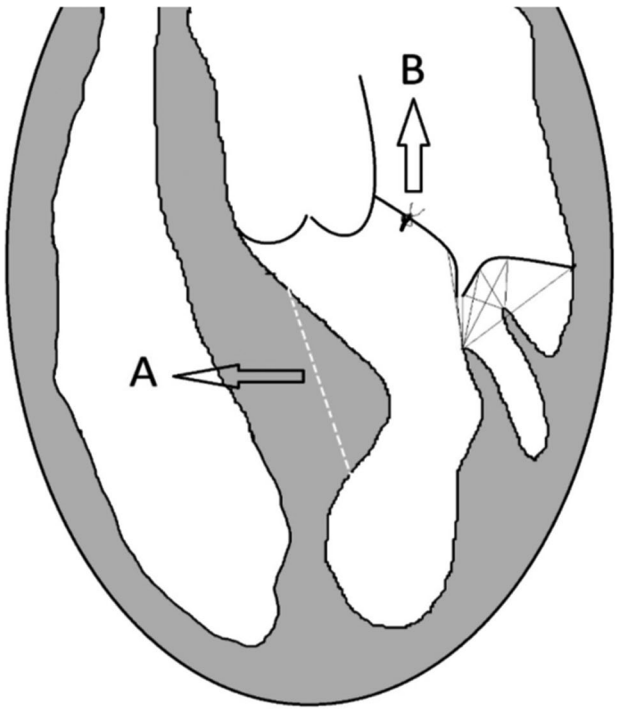

Figure 1. **(a)** Hypertrophic septum. **(b)** Anterior mitral leaflet.

Postoperatively, the patient was followed for one day in the intensive care unit and was, then, transferred to the ward. Control echocardiography showed 1st-2nd degree mitral insufficiency without SAM, and the aortic gradient decreased to 57/23 mmHg. The patient became free from previous complaints. On postoperative Day 8, the patient was discharged and scheduled for follow-up in the outpatient setting. Unfortunately, after about 18 months of the operation, he was found to have 3rd to 4th degree mitral regurgitation and is symptom-free with medical treatment.

DISCUSSION

In general, patients with HOCM may develop LVOT obstruction with diastolic dysfunction, myocardial ischemia, and mitral valve regurgitation. These patients usually present with chief complaints of fatigue, palpitation, syncope or presyncope, and chest pain.[3] Similarly, our patient mainly suffered from fatigue and abdominal pain after meals. There is a strong relation between HOCM and SAM: in early systole, the Bernoulli pressure drops, resulting in the anterior leaflet motion of the mitral valve, while the blood flow of the LVOT decelerates and, then, SAM regression occurs in late systole.[4]

On other hand, the residual leaflet elongation is found to be more likely in patients with SAM of the mitral valve than non-SAM patients. The long posterior leaflet of the mitral valve is considered a strong risk factor for SAM, while the anterior papillary muscle displacement has been identified as a risk factor, as well.[5] In our case, we found that there were secondary chordae of the mitral valve holding the anterior leaflet tightly and long anterior chordae. We resected the secondary chordae and plicated the long anterior charge after septal myectomy.

After mitral repair for mitral valve regurgitation, there is always a possibility of developing regurgitation again or an increase in the degree of regurgitation. In a study conducted by Flameng et al.,[6] even after highly successful repair, the recurrence of mitral valve regurgitation possibility increased over time and occurred at a constant rate, mainly in degenerative valves.[6] In our case, the patient had 3rd to 4th degree mitral regurgitation after about 18 months of surgery, which was 1st to 2nd degree immediately after the operation.

The patient developed mitral regurgitation again after about 18 months. He is still on medication; however, he may need reoperation for valve replacement in the future. In general, repairing the mitral valve apparatus is done through a left atriotomy or, in small left atrium cases, the approach can be achieved via the interatrial septum after right atriotomy.[7] In the cases where aortotomy is done, some prefer performing mitral apparatus repair via aortotomy, particularly when it is associated with septal myectomy.[8] In our case, we preferred performing mitral valve chordae repair via aortotomy and aortic orifice and, the left atrium incision was avoided.

In conclusion, septal wedge myectomy with anterior mitral chordae plication can be done with satisfying results in HOCM associated with SAM cases. However, the possibility of recurrent mitral valve regurgitation over time should be kept in mind.

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Cardiovascular Surgery and Interventions

Review Open Access

Aortoenteric fistulas: A case report and current status

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ABSTRACT

Aortoenteric fistulas are rare, but mostly fatal if left untreated. Diagnosis and treatment are challenging. Aortoenteric fistulas can occur either as a complication of aortic aneurysm or, more commonly, secondary to previous aortic reconstructive surgery. Conventional treatment options are graft excision and extra-anatomic bypass or *in situ* graft replacement. This treatment is associated with high morbidity and mortality rates. Endovascular repair is an emerging therapeutic option. In this article, we describe a case of aortoenteric fistula which was not secondary to a previous reconstructive aortic surgery and discuss the diagnosis and treatment of these fistulas in the light of a comprehensive literature review.

Keywords: Aortoenteric fistula, axillobifemoral bypass graft enteric fistula, graft infection, *in situ* graft.

Aortoentric fistulas (AEFs) are seen rarely, but if left untreated, death is almost inevitable. They usually occur between an aneurysmal segment of the aorta and a neighboring gastrointestinal (GI) structure or between an aortic graft and the intestine in patients having a prior aortoiliac reconstructive surgery.[1] The main symptom in the majority of patients is GI bleeding. Currently, the most commonly used diagnostic tool is computed tomography (CT). The diagnosis can be easily overlooked, as clinical symptoms may vary, radiological findings are generally non-specific, and diagnostic tools have a low sensitivity. A patient who has an aortic aneurysm or a prior aortic surgery and suffers from GI bleeding must be definitely assessed for AEFs. The AEFs are commonly treated with an extra-anatomic bypass (EAB) or *in situ* bypass (ISB), while endovascular treatment has also become an increasing option in recent years. In this article, we present a secondary AEF case developed four years after gynecological surgery with no aneurysm in the aorta or its branches and no aortic prosthesis or graft. We also discuss the diagnosis and treatment of AEFs in the light of a comprehensive literature review.

CASE REPORT

A 56-year-old female patient presented to the emergency department of our hospital complaining about poor general condition and melena. On her physical examination, the blood pressure was 85/50 mmHg and pulse 115/min. No abdominal pain or tenderness was noted. Hemoglobin level was 8.4 mg/dL in the initial complete blood count analysis and 8 mg/dL in the next control carried out 1 h later. Her medical history revealed a history of total abdominal hysterectomy + bilateral salpingo-oophorectomy four years ago. Abdominal ultrasound did not reveal any signs compatible with her complaints and there was no need for emergency colonoscopy and sigmoidoscopy. On abdominal CT, free air was detected in the paraaortic area adjacent to the posterior third part of the duodenum and reduction in the fat plane between the third part of the duodenum and the aorta. Since hyperdense areas suggesting hematoma were also found in the second part of the duodenum, and the patient was assessed for an AEF. A written informed consent was obtained from the patient and she was urgently operated.

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During the operation, retroperitoneum was opened previously, and an AEF was observed to develop in this region between the third part of the duodenum and the left proximal end of the iliac artery. The duodenum was detached and was primarily repaired. The iliac artery was fixed at the proximal and distal parts of the fistula. Then, a suprapubic graft was placed between the right and left femoral artery. The operation was completed in this way; however, since the intestinal content was running from the drains on postoperative Day 4, she was reoperated. The patient was administered intestinal resection and bypass and no other problems occurred during follow-up. When the gynecology department was consulted, the patient was learnt to previously undergo a retroperitoneal lymph node dissection in this region during the initial gynecological surgery. The patient is still alive without any complications at 15 months of her follow-up.

Description

An AEF is an open connection developed between the aorta or its major branches and GI tract. It can develop without any prior aortic intervention, which is called primary AEF (PAEFs), and the first case was published by Salmon in 1843.[2] Its prevalence is between 0.04 and 0.07% in the general population.[3] The PAEFs usually occur between an aneurysmal aortic segment and an adjacent GI structure (73 to 88%); however, they can also develop due to tumors, infections, radiotherapy, peptic ulcers, inflammatory intestinal diseases, and foreign objects without the presence of an aneurysm.[4] A fistula between a vascular prosthesis placed during an aortic surgery and any part of the GI tract is called a secondary AEF (SAEF), which was first described by Brock in 1953.[5] These are more common compared to PAEFs with a reported incidence between 1.6 and 2% after an aortoiliac surgery.[6,7] Its incidence may increase up to 14% after an emergency rupture aneurysm surgery where bacterial contamination and iatrogenic intestinal injuries are more likely.[8]

The SAEFs usually develop due to continuous physical stimulation or infection occurring during an index aortoiliac reconstructive surgery. However, they can also occur in rare cases due to interventions to the aorta or its major branches during surgical procedures performed for other purposes.[9] Another condition which extremely resembles SAEFs, is aortoenteric erosion (AEE). In AEE, the vascular prosthesis leads to erosion on the outer layers of a neighboring GI structure, causing intestinal mucosa to surface. There is a contact between the intestinal mucosa and the prosthetic graft body, but no fistulization. The graft wall is strong enough to prevent any blood passage from the vascular compartment to the GI lumen. The bleeding in AEE usually originates from the intestinal mucosa. In true SAEFs, however, the contact is between the intestine and the anastomotic margin of the graft, which is usually the proximal anastomotic line.[1] The distinction between these two entities is nothing, but a matter of definition. Since the treatment and clinical course of both conditions are almost the same, publications usually address into these two conditions under the same topic. Although the mechanism leading to AEFs has not been elucidated fully, it is thought that the constant pulsatile trauma exerted by the aneurysmal sac to the adjacent structure leads in time to erosion and fistulization in PAEFs. For SAEFs, the agents penetrating the locus from enteric structures that erode through chronic pulsatile stimulus of the prosthetic object and its anastomosed lines or the infection caused by the graft contaminated during the initial surgical intervention are thought to play a key role in the development of a fistula. The inflammation resulting from infection leads to pseudoaneurysms in the anastomotic region, which is the most sensitive part of the vascular structure, followed by formation of a fistula.[3,9-12] The iatrogenic traumas occurring in the intestinal structures during surgery should be also considered in the etiology.

Although AEFs can occur anywhere along the GI tract, more than half of them are seen in the duodenum. The most commonly involved section of the duodenum is its third part.[13] This retroperitoneal part of the duodenum has a fixed location between the Treitz ligament, aorta, and superior mesenteric artery. The closeness of this transverse part of the duodenum to the aorta and proximal anastomosis of the graft makes the duodenum more susceptible to AEF development.

Signs and symptoms

Due to the relationship of AEFs with vascular and intestinal lumens, the most expected symptom in these patients is GI bleeding. A large majority of the patients present with hematemesis (54%) and melena (41%), while other common symptoms are abdominal pain (21%), sepsis (12%), and fever (11%).[13,14] The triad of GI bleeding, abdominal pain,

and pulsatile mass in the abdomen, which was defined by Cooper[15] approximately 200 years ago and agreed to be pathognomonic for PAEF, is seen only in 11% of the patients.[13] Patients with PAEFs and SAEFs usually have the same clinical signs. One of the major characteristics of these patients is that they usually have a herald bleed before the massive GI bleeding occurs. This herald bleed which happens hours or days before the life-threatening bleeding is mostly self-limiting.[16-18] This limitation is thought to be associated with the thrombus forming in the relatively small fistula in the patient who becomes hypotensive due to bleeding. In the following days and hours, this thrombus leaves its place and abundant bleeding starts to take place. Therefore, it is important to avoid aggressive fluid replacement at the time of hospital admission and to keep the systolic blood pressure in the 70 to 100 mmHg interval. In addition, signs of sepsis such as fever, leukocytosis, weakness, and bacteremia are seen in 41%, shock in 46%, and pain in 22% of the patients.[19]

Diagnosis

The most important step in diagnosing AEFs is to keep the suspicion of an AEF in mind. Since AEFs are less common among the causes of GI bleeding, clinicians may not be knowledgeable enough on this pathology, and the signs and symptoms quite differ from case to case, and the sensitivity of imaging methods are relatively low, and the diagnosis is often missed. Therefore, if a patient who presented with complaint of GI bleeding has an aortic aneurysm or a previous aortoiliac surgery, he/she should be considered to have an AEF, until otherwise evidenced.[20] Even if no active bleeding is found in physical examination, such patients should be closely observed and their vital signs continuously monitored, as they usually experience a herald bleed before the onset of their abundant bleeding.[16,17] Currently, the most commonly used imaging method is CT.[21,22] As it is readily available, has relatively easy application and short scan time, and gives a lot of information for the differential diagnosis, CT is the most suitable diagnostic tool for the diagnosis of AEFs. The most important CT finding in AEFs is the gas detected in the aorta or in adjacent regions.[23] However, the presence of gas is not specific to AEF alone. It is normal to find free gas in this region within the first month following an aortoiliac surgery. Gas in this region can be also detected in graft infections without the presence of a fistula. However, any soft tissue, gas or fluid to be found around the graft after Week 7 should be considered as a perigraft infection.[24] The most specific indication is the contrast penetration from the aorta into the intestinal lumen, although this can be detected rarely.[25,26] Penetration of free contrast from the aorta to the surroundings of the graft is again a specific finding; however, this is also encountered quite rarely. Non-specific signs much more commonly found than the aforementioned findings are more useful in making the diagnosis of an AEF. The most frequent signs indicating an AEF include reduced periaortic fat plane, focal thickening, and shrinkage in the neighboring intestinal wall, periaortic free fluid, free gas around the aorta, and pseudoaneurysm at the anastomotic margin.

Although the diagnostic value of gastroduodenoscopy varies in different publications, it can diagnose 25 to 50% of all AEFs.[27] A large majority of AEFs are seen in the third and fourth parts of the duodenum, which makes it technically difficult to advance the endoscope to this region and requires synchronization between operator and patient. Nevertheless, gastroduodenoscopy is quite helpful in differentiating from other causes of GI bleeding.[27] It gives fairly specific results in terms of scintigraphy and 18F-fludeoxyglucose (FDG) positron emission tomography (PET)/CT AEF. However, it is not much practical, since the patient must be in a stable position during the scan. Due to its less availability and longer scan time, magnetic resonance imaging (MRI) is not a highly preferred imaging method in AEFs, yet. Although not primarily a diagnostic tool for AEFs, conventional angiography can be used in patients who are eligible for transcatheter and endovascular interventions.

Treatment

Once diagnosed with an AEF, the patient should be started an empirical antibiotherapy without any delay. Microorganisms of different species are isolated in PAEFs.[3,13,27] One of the most frequently isolated microorganisms is *Candida*.[19] As for bacteria, the most commonly isolated species are *Escherichia coli*, *E. faecalis*, *Salmonella*, *Mycobacterium tuberculosis*, *Clostridium septicum*, *Lactobacillus, and Klebsiella*.[28] However, very few studies provide data on the culprit microorganism. Although studies on SAEFs have reported isolation of many different microorganisms, most of the cases involve *Staphylococcus*, *Streptococcus spp.* and *Escherichi coli*.[28] Apart from these, *Pseudomonas aeruginosa*,

Enterococcus spp., *Veilonella spp.*, *Peptostreptococcus spp.*, *E. Coli*, and *Staphylococcus aureus* have been identified in the mixed flora.[28] Patients diagnosed with an AEF should be immediately started antimicrobial therapy in the postoperative period. The treatment should involve broad-spectrum antibiotics and antifungals covering Gram-positive, Gram-negative, and anaerobic pathogens, as well as *Candida*.

Patients in whom antibiotherapy is arranged should be made ready for a surgical intervention without losing time. Even if they are hemodynamically stable at the time of admission, it should be kept in mind that these patients may have abundant bleeding at any time. The liquid and blood needs of patients who are unstable or in shock should be met immediately. Afterwards, an intervention method suitable for the patient should be selected. Open surgery is a widely used and recommended treatment; however, there are ongoing works on endovascular intervention which has become increasingly popular recently.

ISB versus EAB

The AEFs are conditions which result in death, if left untreated. Since it was first defined, AEFs have been evidenced to require surgery for treatment. The main goal of open surgery is to ascertain the diagnosis, stop bleeding, remove the infected graft, resect the infected tissues as broadly as possible, repair intestinal defect, and allow the blood flow to the distal vascular bed through a vascular prosthesis. Therefore, the EAB method has been used for the treatment of AEFs since early periods, in which the vascular prosthesis is placed away from the infected region. This approach has been agreed to be the gold standard for a long time, but it is not possible to advocate that the results are at a desired level. Several studies have reported mortality rates between 25 and 90% for EAB, major amputation rates between 5 and 25%, and aortic stump rupture rates between 10 and 50%.[9] Since the prolonged surgical time of EAB causes a serious stress in patients with an already poor general condition, the idea of a staged surgery has emerged. In patients with a stable condition, first a lower extremity blooding is achieved through EAB and, in the following days, AEF repair and graft excision are performed. This approach aims at reducing mortality. In a study including patients with aortic graft infection, postoperative mortality was found to decrease to 11%.[29] Many centers have attempted ISB using an infection-resistant graft after removing the infected graft for having a low long-term graft patency, lacking the desired low reinfection rates, and having the risk of aortic stump blow-out. The Texas Houston University has started using ISB for treating AEFs and many researchers have utilized ISB technique using a variety of conduits.[30] In general, prosthetic grafts, cryopreserved grafts, and autologous venous grafts are used for ISB.

Prosthetic grafts have become more favorable over time owing to their low cost and easy availability in various sizes, even in emergency cases. Those prosthetic grafts soaked with rifampin or amikacin or coated with silver to increase their resistance to infections are more preferable. However, there are controversial results with antibiotic-soaked grafts.[31] Grafts soaked with rifampin yield the best outcomes in terms of amputation, conduit failure, and early mortality, although they have the highest reinfection rate.[31] In addition, clinical studies have shown that these grafts are ineffective against methicillin-resistant bacteria such as *Staphylococcus aureus* and *Escherichia coli*.[32] Owing to their silver ion contents, silver-coated grafts are believed to show antimicrobial effects by inhibiting deoxyribonucleic acid replication and protein transcription of messenger ribonucleic acid inside bacterial cells. Although silver-coated grafts have been shown to fail in preventing infections in the *in vitro* setting, some authors have reported promising results.[33,34] Another disadvantage of the prosthetic grafts is their high graft failure and occlusion rates.[35]

Another graft used for ISB is the autologous saphenous graft. Also known as the neoaortoiliac surgical reconstruction, this method aims at restructuring the superficial femoral veins of the lower extremities to make them resistant to aortoiliac system infections. Kakkos et al.[36] found in their study that ISB procedures where lower extremity femoral veins were used had lower mortality rates than the procedures using other grafts. The most favorable outcomes regarding the reinfection rate were also found to be associated with autologous vein grafts.[34] Extremity complications such as edema and compartment syndrome associated with the use of lower extremity deep veins were found within acceptable limits, while only 2% of patients had fasciotomy-requiring edema and permanent leg edema.[37] Since removal of femoral veins takes a long time and prolongs the duration of surgery, it should not be used in patients whose condition is critical, nor should it be used in those having a history of prior deep vein thrombosis.[38] Although many publications report favorable outcomes

with autologous vein grafts, in their 50-case series where they used femoral vein in 34 cases, Chopra et al.[39] reported that the 30-day and 60-day mortality rates were 25% and 48%, respectively.

The results of intestinal repair are independent risk factors affecting survival. Contrary to vascular approach, there is a consensus on intestinal repair. Minor intestinal defects can be repaired outright. In larger defects, however, complex surgeries should not be avoided in fear of leakage and reinfection.[40] Since mortality from reinfection is 100%,[19] it is of vital importance to repair any intestinal leakage most effectively during the first session. Emergence of intestinal complications shows a homogeneous distribution within the first 60 days with an apparent decline, thereafter. Thus, caution should be exercised during the first 60 days for early mortality in AEF cases.[38]

Endovascular repair

In recent years, many studies have been published regarding the outcomes of endovascular intervention in AEFs.[36,41] This approach has been used more frequently in patients who are ineligible for open surgery due to anatomic inconvenience or poor general condition. This method allows a much less invasive approach to closure of the fistula and prevention of bleeding. However, contrary to open surgery, it makes no contribution to the treatment of infection. Therefore, a serious risk of infection continues for the newly placed endovascular prosthesis. Review of the literature on EVAR results reveals a significant superiority to open surgery in terms of early mortality, but such a superiority disappears in the follow-up period.[36] As endovascular treatment does not involve intestinal repair, it should not be considered as a destination treatment. In a 13-month follow-up study, Antoniau et al.[42] reported reinfection and bleeding in 44% of the patients who were administered EVAR for AEFs. In ineligible patients, therefore, EVAR should be considered as a bridging treatment, until the patient becomes ready for open surgery, which should be administered as soon as the patient becomes eligible for it. However, used as the first-line treatment, EVAR may render *in situ* repair more complicated. Moreover, since the fistula originates mostly from proximal anastomosis, insertion of an endograft may pose a risk for the perfusion of renal arteries.

In conclusion, an AEF is a complication resulting in death, if left unrepaired. It should be kept in mind that patients who present in a stable condition may be lost due to abundant bleeding at any time; thus, a surgical intervention should be performed as soon as possible. The AEB, which has been agreed to be the gold standard in the treatment of AEFs for a long time, is now being replaced by ISB thanks to its superior results in the recent publications. Of note, no consensus has been reached yet for the grafts to be used for ISB, and none of the currently used grafts has produced a desirable outcome. Endovascular interventions which have become increasingly popular in recent years should be only used for bridging to open surgery. Performing an intestinal repair in a safe way is of vital importance. Successfully treated patients should be very closely monitored for the first 60 days for possible reinfection and bleeding.

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