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Prior left ventricular systolic dysfunction is an independent predictor of in-hospital mortality in patients with COVID-19

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ABSTRACT

Objectives: This study aims to examine the effect of left ventricular systolic dysfunction (LVSD) on in-hospital mortality in patients hospitalized for novel coronavirus disease 2019 (COVID-19).

Patients and methods: Between June 2020 and December 2020, a total of 847 patients (423 males, 424 females; median age: 68 years; range, 58 to 77 years) who had echocardiography and had positive real-time reverse transcriptase-polymerase chain reaction were retrospectively analyzed. A left ventricular ejection fraction (LVEF%) of <50% was defined as LVSD.

Results: In 138 patients, LVEF was <50% and in 709 patients LVEF was >50% (non-LVSD). Of the patients with LVSD, 89 had mid-range LVEF (40 to 49%), and 49 had reduced LVEF (LVEF <40%). Intensive care unit admission (p<0.001), myocardial injury (p<0.001), and mechanical ventilation (p<0.001) were more frequent in patients with LVSD, and LVSD was found to significantly increase the risk of and in-hospital mortality (odds ratio=2.57, 95% confidence interval, 1.43-4.60, p=0.002). Among patients with LVSD, no significant difference was observed in terms of in-hospital mortality between patients with mid-range LVEF and patients with reduced LVEF.

Conclusion: Our study results showed that LVSD significantly increased the risk of in-hospital mortality in patients hospitalized for COVID-19. In addition, an increased risk of in-hospital mortality was present in both the mid-range LVEF and the reduced LVEF group, separately.

Keywords: COVID-19, in-hospital mortality, left ventricular systolic dysfunction.

Novel coronavirus disease 2019 (COVID-19) remains an important cause of mortality.[1] It may cause mild respiratory tract infection, as well as severe pneumonia and acute respiratory distress syndrome. Besides, it can cause failure in many organs such as the heart, kidney, and liver, and can cause death.[2,3] Complications such as myocarditis, heart failure (HF), arrhythmias, and myocardial ischemia can occur, and high mortality can be seen in these patient groups.[4-6]

Cardiovascular (CV) disease and classical CV risk factors are common comorbidities in COVID-19 patients and have been associated with poor outcomes.[2] Heart failure, one of these comorbidities, is one of the leading causes of death in the world. Respiratory infections are one of the most common factors that trigger decompensation in HF patients and are independently associated with hospital mortality.[7,8] Also, COVID-19 patients with HF have been found to have a predisposition to acute decompensation.[9] Small-scale studies evaluating left ventricular (LV) functions with echocardiography in COVID-19 patients found that the disease was more severe, and mortality was higher in patients with decreased LV functions.[6,10]

In the literature, there are not sufficient data regarding the prognosis of COVID-19 in patients with previously known LV systolic dysfunction (LVSD). In this study, we aimed to examine the effect of prior LVSD on in-hospital mortality in patients hospitalized with COVID-19.

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PATIENTS AND METHODS

This single-center, retrospective, observational study was conducted at University of Health Sciences Diyarbakır Gazi Yaşargil Education and Research Hospital, Department of Cardiology between June 1st, 2020 and December 31st, 2020. Patients aged >18 years hospitalized for COVID-19 pneumonia were evaluated. Patients who had transthoracic echocardiography and had positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) were screened for the study. Patients who had negative RT-PCR results were excluded from the study. Patients who did not have echocardiography and those hospitalized for reasons that may affect LV ejection fraction (LVEF), such as myocardial infarction (MI) and myocarditis after the date of echocardiography were excluded from the study. Also, patients who developed new LVSD due to MI, stress cardiomyopathy, and myocarditis while being followed with COVID-19 were excluded from the study. A total of 5,920 patients were screened for the study, and 847 patients (423 males, 424 females; median age: 68 years; range, 58 to 77 years) were included in the study. The study flow chart is shown in Figure 1. The study protocol was approved by the University of Health Sciences Diyarbakır Gazi Yaşargil Education and Research Hospital Ethics Committee (date/no: 26.03.2021/737). The study was conducted in accordance with the principles of the Declaration of Helsinki.

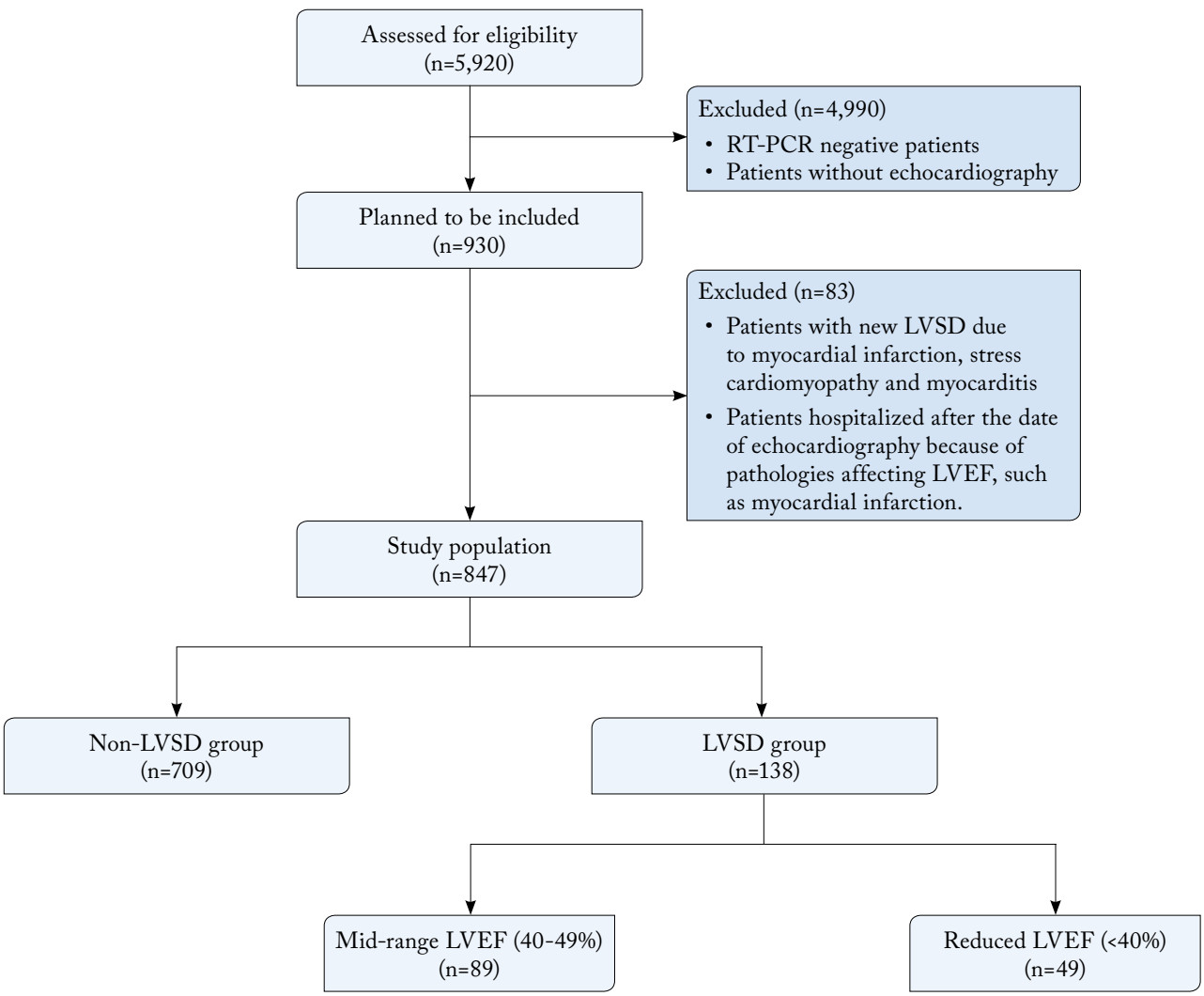

Figure 1. Study flow chart.

RT-PCR: Real-time reverse transcriptase-polymerase chain reaction; LVSD: Left ventricular systolic dysfunction; LVEF: Left ventricular ejection fraction.

Table 1
Demographic, clinical characteristics, laboratory findings and outcomes of the study population

	Total (n=847)				Non-LVSD (n=709)				LVSD (n=138)				
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
Age (year)			68	58-77			66	57-75			73	67-82	<0.001
Sex													
Female	424	50.1			368	51.9			56	40.1			0.015
Comorbidities													
Hypertension	521	61.5			405	57.1			116	84.1			<0.001
Diabetes mellitus	270	31.9			215	30.3			55	39.9			0.028
Coronary artery disease	334	39.4			222	31.3			112	81.2			<0.001
Chronic obstructive pulmonary disease	115	13.6			86	12.1			29	21			0.008
Chronic renal failure	46	5.4			34	4.8			12	8.7			0.100
Atrial fibrillation	50	5.9			32	4.5			18	13			<0.001
Stroke	56	6.6			46	6.5			10	7.2			0.888
Malignancy	47	5.5			44	6.2			3	2.2			0.091
Ejection fraction (%)			60	55-60			60	58-63			43	36-45	
Myocardial injury	84	9.9			56	7.9			28	20.3			<0.001
Symptoms													
Weakness/fatigue	395	46.6			322	45.4			73	52.9			0.107
Cough	400	47.2			343	48.4			57	41.3			0.128
Shortness of breath	671	79.2			554	78.1			117	84.8			0.078
Fever	275	32.5			224	31.6			51	37			0.218
Clinical finding													
Oxygen saturation (%)			88	82-91			88	82-91			86	80-90	0.024
Heart rate (beat/min)			85	76-95			85	76-95			85	76-96	0.768
Temperature (°C)			36.7	36.5-37.0			36.7	36.4-37.0			36.7	36.5-37.1	0.006
Systolic blood pressure (mmHg)			120	110-130			120	110-127			120	110-130	0.083
Diastolic blood pressure (mmHg)			70	60-80			70	60-80			70	61-80	
Laboratory													
White blood cell (10^3/uL)			7.52	5.50-10.65			7.28	5.49-10.24			8.53	6.10-13.41	0.004
Neutrophil (10^3/uL)			5.80	3.95-8.77			5.59	3.88-8.16			6.87	4.35-11.42	0.001
Lymphocyte (10^3/uL)			1.03	0.71-1.49			1.05	0.72-1.49			0.97	0.65-1.46	0.061
Hemoglobin (g/dL)			13.1	11.914.4			13.2	12.0-14.4			12.7	11.0-14.2	0.012
Platelet (10^3/uL)			212	168-265			213	170-259			210	152-282	0.484
C-reactive protein (mg/L)			84	41-144			84	41-141			83	40-155	0.674
D-dimer (ng/mL)			303	196-611			289	190-538			395	249-878	<0.001
Ferritin (µg/L)			433	214-871			433	214-865			458	215-879	0.845
Lactate dehydrogenase (IU/L)			327	256-434			330	257-435			307	253-431	0.338
Procalsitonin (ng/mL)			0.12	0.07-0.33			0.11	0.07-0.29			0.21	0.10-0.64	<0.001
Troponin (ng/mL)			0.1	0.1-0.1			0.1	0.1-0.1			0.1	0.1-0.12	<0.001
Creatinine (mg/dl)			1.00	0.79-1.43			0.93	0.78-1.34			1.35	0.98-2.03	<0.001
Alanin transaminaz (U/L)			22	15-36			23	15-37			18	13-30	0.001
Albumin (g/L)			31	28-35			32	28-35			29	27-32	<0.001
Sodium (mmol/L)			136	133-139			136	134-139			135	133-139	0.096
Total calcium (mg/dL)			8.2	7.8-8.6			8.2	7.8-8.6			8.1	7.7-8.5	0.064
Potassium (mmol/L)			4.21	3.87-4.66			4.18	3.86-4.62			4.47	4.00-4.90	<0.001

Table 1
Continued

	Total (n=847)				Non-LVSD (n=709)				LVSD (n=138)				
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
Pre-hospitalization medications													
Beta-blockers	366	43.2			263	37.1			103	74.6			<0.001
RAAS inhibitors	480	56.7			372	52.5			108	78.3			<0.001
Calcium channel blockers	276	32.6			225	31.7			51	37			0.231
Thiazide	278	32.8			223	31.5			55	39.9			0.054
Mineralocorticoid receptor antagonist	37	4.4			14	2			23	16.7			<0.001
Loop diuretic	86	10.2			34	4.8			52	37.7			<0.001
Antiplatelet	411	48.5			306	43.2			105	76.1			<0.001
Oral anticoagulant	41	4.8			22	3.1			19	13.8			<0.001
Statin	182	21.5			132	18.6			50	36.2			<0.001
In-hospital medication													
Anticoagulant	766	90.4			640	90.3			126	91.3			0.825
Favipiravir	759	89.6			637	89.8			122	88.4			0.723
Tocilizumab	49	5.8			44	6.2			6	4.3			0.321
Steroids	602	71.1			504	71.1			98	71			0.986
Vasopressor	114	13.5			85	12			29	21			0.007
IV diuretic	135	15.9			66	9.3			69	50			<0.001
Nasal oxygen	652	77			542	76.4			110	79.7			0.405
Outcomes													
Intensive care unit admission	299	35.3			227	32			72	52.2			<0.001
Length of stay hospital (day)			8	6-12			8	6-12			9	6-13	0.181
Mechanical ventilation	218	25.7			154	21.7			64	46.4			<0.001
All cause in-hospital mortality	187	22.1			129	18.2			58	42			<0.001

IQR: Interquartile range; LVSD: Left ventricular systolic dysfunction; RAAS: Renin-angiotensin-aldosterone system; Renin-angiotensin-aldosterone system inhibitors.

The demographic, clinical characteristics and laboratory parameters, comorbidities, hospitalization time of the patients during hospitalization were collected from the electronic medical records of the hospital and national electronic medical record system. We have obtained other hospital admissions from these national records.

The LVEF% was measured by the biplane Simpson method or Teicholz method.[11] In addition, LVSD was calculated as an LVEF of <50%. Mid-range LVEF (40 to 49%) and reduced LVEF (<40%) were calculated according to the European Society of Cardiology (ESC) Heart failure guidelines.[12] Myocardial injury was defined as the presence of at least one cardiac troponin value above the 99th percentile upper reference limit.[13] The study outcome was in-hospital mortality.

The primary outcome measure of the study was in-hospital mortality.

Statistical analysis

Statistical analysis was performed using the "rms", "Hmisc", and "ggplot2" packages with R studio version 4.02 (R Project, Vienna, Austria). Continuous variables were presented in median and interquartile range (IQR, 25th-75th). Categorical variables were presented in number and frequency. The chi-square test was used to compare categorical variables between groups. Continuous variables were compared using the Mann-Whitney U tests. A p value of <0.05 was considered statistically significant.

We used the logistic regression method to investigate the relationship between primary outcome and candidate predictors. Effects of individual

Table 2
Univariate and multivariate logistic regression analyses for predictors of in-hospital mortality

	Univariable analysis			Multivariable analysis		
Variables	OR	95% CI	p	OR	95% CI	p
Age (year)	1.05	1.04-1.07	<0.001	1.05	1.03-1.07	<0.001
Sex						
Male	1.24	0.89-1.71	0.201			
Hypertension	1.48	1.05-2.09	0.027	0.98	0.59-1.62	0.934
Diabetes mellitus	1.55	1.10-2.17	0.011	2.08	1.29-3.36	0.003
Coronary artery disease	1.77	1.28-2.46	0.001	1.21	0.75-1.98	0.437
Left ventricular systolic dysfunction	3.30	2.34-4.87	<0.001	2.57	1.43-4.60	0.002
Atrial fibrillation	1.90	1.03-3.49	0.039	1.12	0.50-2.51	0.790
Chronic obstructive pulmonary disease	1.43	0.918-2.23	0.113			
Chronic renal failure	1.77	0.93-3.35	0.081			
Myocardial injury	5.810	3.63-9.31	<0.001	3.30	1.68-6.45	<0.001
Creatinine (mg/dL)	1.11	1.01-121	0.023	1.02	0.89-1.16	0.785
White blood cell (10^3/uL)	1.09	1.05-1.12	<0.001	0.97	0.94-1.03	0.555
Lymphocyte (10^3/uL)	0.65	0.71-2.43	0.003	0.89	0.66-1.20	0.461
D-dimer (ng/mL) (per 100 units increase)	1.02	1.01-1.03	<0.001	1.01	1.00-1.02	0.013
LDH (U/L) (per 10 units increase)	1.03	1.02-1.04	<0.001	1.01	1.00-1.02	0.194
CRP (mg/L) (per 10 units increase)	1.07	1.05-1.09	<0.001	0.99	0.96-1.03	0.696
Oxygen saturation (%)	0.84	0.82-0.87	<0.001	0.85	0.82-0.87	<0.001
Heart rate (beat/min)	1.03	1.01-1.04	<0.001	1.02	1.00-1.03	0.012
Malignancy	1.22	0.67-2.40	0.561			
Cerebrovascular event	1.31	0.71-2.43	0.384			
Systolic blood pressure (mmHg)	1.07	1.00-1.02	0.248			

OR: Odds ratio; CI: Confidence interval; LDH: Lactate dehydrogenase; CRP: C-reactive protein.

predictors were reported using odds ratio [OR] and 95% confidence interval [CI].

We selected predictive candidate variables based on existing studies and known or plausible associations with COVID-19 infection morbidity and mortality.[14,15] Variables (age, sex, cerebrovascular event, malignancy, hypertension, diabetes mellitus [DM], coronary artery disease, atrial fibrillation, chronic renal failure, chronic obstructive pulmonary disease, myocardial injury, systolic blood pressure, heart rate, oxygen saturation, white blood count, lymphocytes, creatinine, lactate dehydrogenase, C-reactive protein, D-dimer) were used in regression analysis. Univariate and multivariate logistic regression analyses were performed to determine the effect of LVSD on in-hospital mortality. Variables with a p value of <0.05 in the univariate analysis were added to the model in the multivariate analysis. Furthermore, LVSD was added to the full model first as two groups (LVSD and non-LVSD) and, then, as three groups (mid-LVEF, reduced LVEF, and non-LVSD). Adjusted variable three-dimensional (3D) plot of the model was performed to predict outcome (mortality) probabilities according to age scores and LVSD.

RESULTS

A total of 847 patients, including 709 (83.8%) non-LVSD and 138 (16.2%) LVSD patients, were included in the study. Intensive care unit admission (52.1% *vs.* 32%), myocardial injury (20% *vs.* 8%), mechanical ventilation (46% *vs.* 22%), and death (42% *vs.* 18%) were higher in the LVSD group. The demographic, clinical characteristics, laboratory findings, and outcomes of the study population are given in Table 1.

Mortality was significantly higher in the LVSD group than in the non-LVSD group, and LVSD significantly increased the risk of in-hospital mortality in the multivariate logistic regression analysis (OR=2.57, 95% CI: 1.43-4.60, p=0.002). When LVSD was added to the model as two separate groups, both mid-range LVEF and reduced LVEF was observed as independent predictors of in-hospital mortality (OR= 2.66, 95% CI: 1.38-5.14 p=0.004, OR=2.39 95% CI: 1.02-5.62, p=0.046, respectively). Age, myocardial injury, DM, D-dimer, heart rate, and oxygen saturation were other parameters that significantly increased in-hospital mortality risk. Univariate and multivariate logistic regression analyses were performed to evaluate the effect of LVSD on in-hospital mortality (Table 2). Figure 2 shows adjusted variable 3D plots of the full model, predicted probabilities of mortality according to age and LVSD presence.

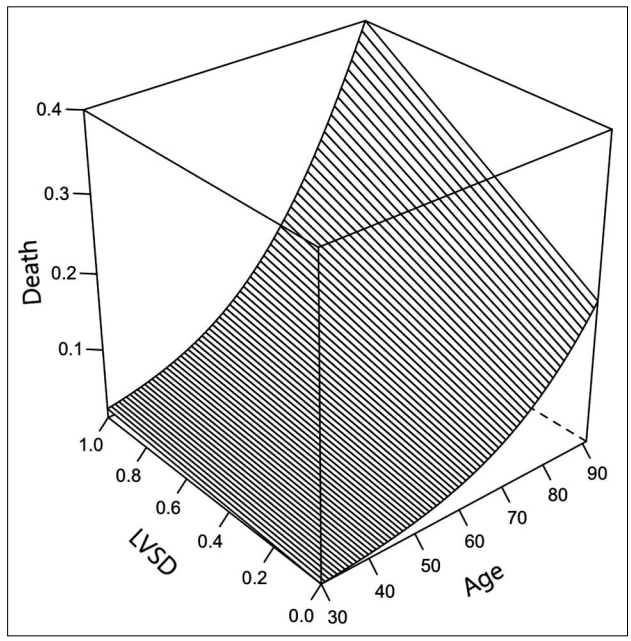

Figure 2. Three-dimensional plot showing the effect of age and LVSD on in-hospital mortality after adjustment with clinical predictors.
LVSD: Left ventricular systolic dysfunction.

DISCUSSION

According to the results of this study, LVSD was associated with poor outcomes and it was found to be an independent predictor of in-hospital mortality and an approximately 2.6-fold increase in risk was observed, after adjustment with multivariate analysis. No significant difference was observed in mid-range LVEF and reduced LVEF groups in terms of in-hospital mortality, and the mortality risk increased significantly in both groups in the regression analysis, compared to the non-LVSD group.

Although COVID-19 infection begins as a respiratory tract infection, pathological findings can often occur in many organs and tissues, such as the heart. In the studies conducted, the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was seen in macrophages, endothelial cells, and pericytes, and in the autopsy series, evidence of viral replication in myocardial cells was obtained.[16] Conditions such as the increased risk of MI, fulminant

myocarditis, arrhythmias, venous thromboembolism, and Takotsubo cardiomyopathy are the most common CV complications identified in COVID-19 patients.[17] In addition to direct myocardial damage caused by the virus by binding to the angiotensin-converting enzyme 2 (ACE-2) receptor, which is important for cardiac functions, causing ACE-2 receptor downregulation, the release of inflammatory mediators, endothelial dysfunction, and myocardial damage due to micro- and macro-thrombi may play a role in the occurrence of these complications.[18-20] Myocardial injury, defined by the increased troponin levels, presented mortality greater than those without myocardial injury, is an independent risk factor for mortality.[15] In our study, the myocardial injury was observed as the independent predictor of mortality (OR=3.30, p<0.001). Arterial and venous thrombosis can be seen in COVID-19.[21] Studies have found that elevated D-dimer increases the risk of mortality.[22] In our study, a significant increase was observed in-hospital mortality risk with elevated D-dimer. Also, age, DM, heart rate, and oxygen saturation were other factors that significantly increased the risk of in-hospital mortality.

Cardiovascular diseases are among the most common comorbidities in patients hospitalized with COVID-19 and are associated with poor outcomes.[2] Heart failure is one of the important causes of morbidity and mortality, particularly in advanced ages. Conditions such as upper respiratory tract infection and pneumonia may cause decompensation in these patient groups.[7,8] It has been observed that COVID-19 infection, which is a respiratory tract infection, also predisposes to decompensation.[9] In a small-scale study comparing the patients hospitalized due to HF with and without COVID-19 infection, mortality was approximately five times higher in those with COVID-19 infection.[23] Again, in a study by Alvarez-Garcia et al.,[14] the effect of HF on in-hospital death in COVID-19 patients was examined and HF increased mortality significantly, regardless of LVEF, and mortality was observed at a rate of approximately 40% in the group with HF. In our study, LVSD (both in the mid-range LVEF and reduced LVEF groups) was found to be an independent predictor of in-hospital mortality, with a 2.6-fold increase in risk with LVSD, and 42% of patients died during in-hospital follow-up. According to the results of our study, the frequency of myocardial injury was observed more in the LVSD group, which is one of the predictors of mortality. The SARS-CoV-2 may predispose to stress cardiomyopathy and cytokine-induced myocardial dysfunction and, as a result, acute decompensation of congestive heart failure may worsen subclinical pre-existing injury in well-compensated patients.[24] The increase in mortality in these patient groups may be due to myocardial damage caused by the direct effect of the virus, inflammatory response, hypoxia, and endothelial dysfunction worsening LV systolic functions and decompensation.

Heart failure patients are the groups that require special care during hospitalization. Mortality was found to be significantly higher in COVID-19 patients with HF, both with the results of other studies and the results of our study. Perhaps due to the density of hospitals caused by the pandemic, the inability to pay close attention to these patients may have contributed to the increase in mortality. Among LVSD patients included in the study, the number of patients who did not have optimal HF treatment during hospitalization was not small. A study showed that discontinuation of HF treatment during hospitalization caused a significant increase in in-hospital mortality.[9] Therefore, close follow-up of patients hospitalized for COVID-19 with LVSD and providing optimal treatment may reduce high mortality rates.

This study has some limitations, including the small number of LVSD patients from a single center with a retrospective design. Another limitation is that obesity and New York Heart Association (NYHA) classes cannot be included in the multivariate analysis due to insufficient data. As brain natriuretic peptide levels were not studied and diastolic dysfunction parameters were not evaluated in detail in most patients, HF patients with preserved ejection fraction could not be excluded from the study. The inability to determine the intensive care admissions as the outcome is another limitation. This is because severe patients cannot be taken into intensive care due to the lack of enough beds during the peak periods of the disease.

In conclusion, LVSD was an independent predictor of in-hospital mortality in our study. An increased risk of in-hospital mortality was present in both the mid-range LVEF and the reduced LVEF group, separately. In addition, myocardial injury, older age, DM, D-dimer, oxygen saturation, and heart rate were other independent predictors of in-hospital mortality.

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Original Article Open Access

Comparison of Doppler ultrasonography and computed tomography angiography for endoleak diagnosis after endovascular treatment of abdominal aortic aneurysm

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ABSTRACT

Objectives: This study aims to compare the utility of Doppler ultrasound (DUS) versus computed tomography angiography (CTA) in the diagnosis of endoleaks.

Patients and methods: Between October 2008 and December 2010, a total of 30 patients (27 males, 3 females; mean age: 70.1±12 years, range: 52 to 85 years) with abdominal aortic aneurysms (AAAs) who underwent endovascular aneurysm repair (EVAR) were retrospectively analyzed. All patients were followed at 1, 6, and 12 months after EVAR with both DUS and CTA.

Results: Stents grafts were patent in all patients. Endoleak was detected with CTA in six patients. Four patients had type I endoleak and two had type 2 endoleak. On CTA, two patients with type 2 endoleaks were unable to be detected with DUS. Considering CTA as the gold standard, DUS had a sensitivity and specificity of 75% and 100%, respectively. For detecting type 1 endoleak, DUS demonstrated a sensitivity and specificity of 100% and 100%, respectively. For detecting type 2 endoleak, DUS had a sensitivity of 50% and specificity of 100%.

Conclusion: Our study results suggest that DUS is reliable method for detecting endoleak and measuring diameter of aneurysm during follow-up after EVAR. It may be possible to use DUS as an alternative to CTA in routine follow-up of the patients.

Keywords: Aneurysm, computed tomography angiography, Doppler ultrasound, endoleaks, endovascular aneurysm repair.

Abdominal aortic aneurysm (AAA) is pathological dilation of the abdominal aorta which is susceptible for rupture and ranks the 13th leading cause of death in the United States.[1,2] Major risk factors for aneurysm rupture are female sex, aneurysm diameter, growth rate (more than 1 cm per year), chronic obstructive pulmonary disease, low forced expiratory volume in 1 sec (FEV1), current smoking status, family history, connective tissue disease, and elevated mean arterial pressure.[3,4]

Ultrasound (US) and Doppler US (DUS) are used to show the diameter of the aneurysm, its longitudinal size, its relationship with the renal artery, the presence of mural thrombus, and its extension to the iliac arteries.[5,6] If surgery is planned, computed tomography (CT), computed tomography angiography (CTA), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), digital subtraction angiography are the choices.[7]

Apart from non-operative follow-up, there are two options for elective repair of AAA: open surgical treatment (OST) and repair with endovascular aneurysm repair (EVAR) to prevent rupture.[8] Surgery should be performed in low medical risk, active life of patients with aneurysm diameter greater than 5.5 cm, or symptomatic and rapidly growing aneurysms (0.5 cm within six months, over 1 cm in a year), regardless of diameter or diameter of ≥6 cm.[9] Compared to conventional surgery, EVAR has many advantages such as shorter procedure time, low morbidity, mortality

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and paraplegia rates, short intensive care unit duration, and lower rates of renal, cerebral and respiratory complications.[2,10,11] On the other hand, OST has lower rates of re-operation with lower long-term mortality rates.[12]

Contrast medium reaction, contrast medium-induced renal insufficiency, colonic ischemia, wound complications, renal failure, myocardial infarction, pneumonia and death are perioperative complications of EVAR.[2,10,13,14] Long-term complications of the technique are endoleaks, graft infection, aortoenteric fistula, buttock claudication, limb occlusion, and sexual dysfunction.[2,10] The most common complication of EVAR is endoleaks, which is the leakage of blood between the graft and the aneurysm sac and is asymptomatic until aneurysm sac ruptures occur.[13]

Currently, CTA is the most commonly used gold-standard imaging modality in the diagnosis of endoleaks and in post-repair follow-up with EVAR. In the present study, we aimed to investigate the diagnostic accuracy of DUS versus CTA for the detection of endoleaks after EVAR in the early follow-up period.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Izmir Katip Çelebi University, Faculty of Medicine, Department of Cardiovascular Surgery between October 2008 and December 2010. Patients who were diagnosed with AAA and underwent endovascular stent graft application were screened using the hospital database. Patients with ruptured AAAs, previous open abdominal vascular surgery history, AAAs extending above the renal arteries, and those who were not eligible for endovascular intervention were excluded. Finally, a total of 30 patients (27 males, 3 females; mean age: 70.1±12 years, range: 52 to 85 years) who were followed with both DUS and CTA after treatment were included. A written informed consent was obtained from each patient. The study protocol was approved by the Izmir Katip Çelebi University, Faculty of Medicine Ethics Committee (Date/no: 2021/0019). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Endovascular stent graft placement was performed under local anesthesia in 16 patients, general anesthesia in 11 patients, and epidural anesthesia in the remaining three patients. Femoral access was used in all patients and self-expandable monotype graft was preferred. An aorto-uni-iliac stent graft was placed in four patients, contralateral iliac artery was occluded, and femoro-femoral bypass was applied in these patients. An aorto-bi-iliac stent graft was placed in the other 26 patients. Approximately 10 to 20% oversizing was applied to preoperative calculated size of proximal and distal landing zones. An interventional radiologist and vascular surgeon performed the procedures simultaneously. The patients were followed at 1, 6, and 12 months after EVAR with both DUS and CTA.

Computed tomography angiography technique

All patients underwent CTA examination with an aneurysm protocol on a four-detector CTA device (Toshiba Corp., Tokyo, Japan). Contrast material was administered through the antecubital route with an automatic injector. Axial sections in the arterial phase were obtained from the diaphragm level to the iliac bifurcation after an average of 100 mL of non-ionic contrast material administration at a rate of 3 mL/s with the bolus tracking technique. Sagittal and coronal images were reconstructed from axial images. Aneurysm diameter measurement was performed on these reconstructed reformat images. Considering the course of the aorta, transverse diameter was measured from the widest part of the aneurysm. In the captured CTA protocol, the slice thickness was 3 mm, pitch: 1, rotation time 0.5 sec, kV: 120, mA: 250. Images were sent to Picture Archiving and Communication System (PACS) and workstation after shooting. Evaluation was made at workstations and all images were archived in the PACS (Figure 1).

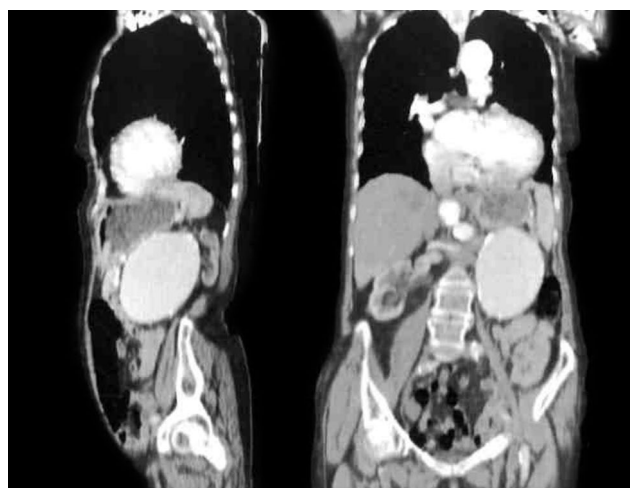

Figure 1. Computed tomography angiography of sagittal and coronal reformat images.

Doppler ultrasound technique

Doppler US examination of the abdominal aorta and its branches was performed in all patients in the supine position, with breath holding or during shallow breathing in patients who could not hold their breath. Investigations were performed using a 3 to 5 MHz multifrequency probe on a Logiq™ P6 device (General Electric Co., NY, USA). The images obtained after the examination were archived. All DUS examinations were performed by a radiologist experienced in DUS. Aneurysm and stent graft were examined in axial and longitudinal planes with B-mode and DUS. The transverse diameter of the aneurysm, perpendicular to the course of the vessel, was measured at the widest part of the aneurysm (Figure 2). The presence of flow in the lumen of the aneurysm other than the lumen of the stent, the presence of color coding in DUS, whether this flow is related to the aortic branches and the patency of the graft lumens were investigated in cases with flow outside the stent lumen.

Routine CTA and DUS results were compared considering the presence of endoleak, aneurysm diameter, and stent patency. This comparison was made by two separate radiologists who evaluated routine CTA scans and performed DUS examination.

Statistical analysis

Statistical analysis was performed using the SPSS 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, where applicable. One sample t-test was used to analyze variables, while the Kappa agreement analysis and receiver operating characteristics (ROC) curve analysis were used for the agreement on endoleaks detection between DUS and CTA. The Pearson correlation analysis was used to evaluate the correlation between the variables. The difference between DUS and CTA diameter measurements was examined using the Student's t-test. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of DUS for endoleak detection were calculated by accepting CTA as the gold standard. A p value of <0.05 was considered statistically significant.

RESULTS

Demographic characteristics of the patients included in the study are summarized in Table 1. The mean follow-up period was 8.6±3 months. In all of our patients, the first CTA and DUS examinations were performed within the first week before discharge. Eighteen (60%) patients were further evaluated with CTA and DUS at both 6 and 12 months of the follow-up, eight (26.67%) patients were evaluated with CTA and DUS at six months, and four (13.33%) patients were evaluated with CTA and DUS at 12 months. The stent graft was patent in all patients. Endoleak was detected in six patients (20%) on CTA examination.

Three patients diagnosed with type 1A endoleak on DUS were also diagnosed with type 1A endoleak

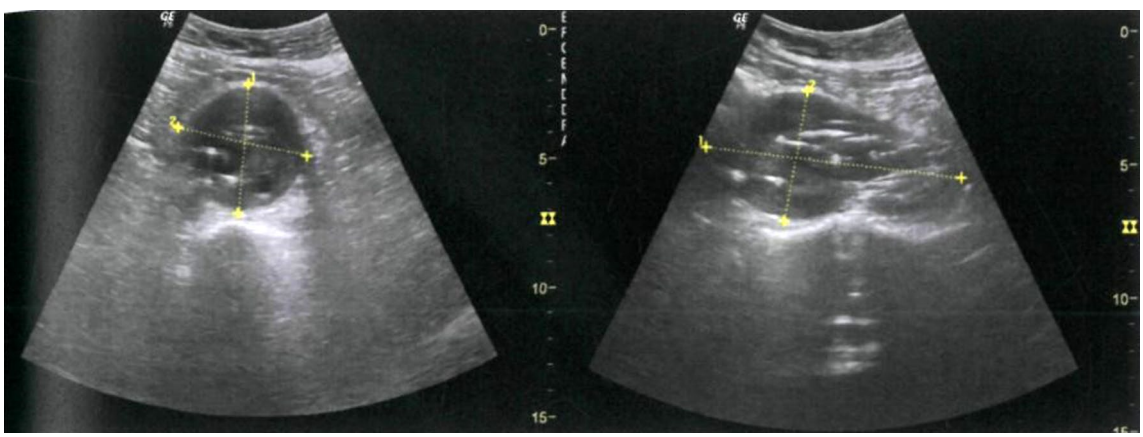

Figure 2. Size measurements of the aneurysm sac in images perpendicular and parallel to the long axis, respectively with DUS.
DUS: Doppler ultrasonography.

Table 1
Demographic characteristics of patients

No	Age	Sex	Comorbidity	Operation	Aneurysm diameter (CTA) (mm)	Aneurysm diameter (DUS) (mm)
1	59	M	HT, DM, COPD	-	64	6
2	76	M	CAD, PAH, HT	CABG	74	69
3	71	M	PAH, HT	-	65	65
4	71	M	HT, CAD	CABG	56	50
5	78	M	CAD, HT, COPD	CABG	63	60
6	85	M	CAD, HT	-	100	93
7	81	M	DM, HT	-	60	63
8	58	M	HT, CAD	CABG	55	52
9	54	M	HT, Ehler Danlos	-	92	90
10	82	M	DM, HT, CAD	CABG	62	60
11	80	M	COPD, HT	-	58	55
12	67	M	HT, CAD	CABG	98	96
13	82	F	HT	-	55	52
14	54	M	HT, Crohn	-	60	57
15	72	M	HT, COPD	-	60	58
16	80	M	HT	-	65	62
17	79	M	HT	-	54	50
18	72	F	-	-	70	66
19	52	M	-	-	93	89
20	63	M	CAD, COPD	-	75	72
21	71	M	HT	-	60	58
22	62	M	HT, PAH		52	51
23	60	M	DM, HT	-	56	52
24	62	M	HT, CAD	CABG	79	80
25	80	M	HT	-	45	45
26	82	M	-		53	50
27	75	M	CAD, PAH	CABG	67	66
28	84	M	COPD	-	57	53
29	84	F	-	-	65	67
30	76	M	DM, HT	-	66	64

CTA: Computed tomography; DUS: Doppler ultrasound; HT: Hypertension; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; PAH: Pulmonary artery hypertension; CABG: Coronary artery bypass graft.

on CTA and 27 patients who were thought not having type 1A endoleak on DUS were not type 1A endoleaks on CTA, either (Table 2). The Kappa coefficient calculated for the positive and negative values for the diagnosis of type 1A endoleak was found to be 1,000 (p=0.000), and a perfect agreement was observed between DUS and CTA results which were statistically significant according to the ROC curve analysis (p<0.001) (Figure 3, Table 3).

One patient who was diagnosed with type 1B endoleak on DUS was also diagnosed with type 1B endoleak on CTA. Again, all 29 cases who were thought to be negative for type 1B endoleak on DUS were also negative on CTA for type 1B endoleaks,

Table 2
Diagnosis of endoleak type according to imaging procedures

	CTA (+)	CTA (-)
Type 1A endoleak		
DUS (+)	3	0
DUS (-)	0	27
Type 1B endoleak		
DUS (+)	1	0
DUS (-)	0	29
Type 2 endoleak		
DUS (+)	2	0
DUS (-)	2	26

CTA: Computed tomography angiography; US: Ultrasonography.

either (Table 2). The Kappa coefficient calculated for the positive and negative values for the diagnosis of type 1B endoleak was found to be 1,000 (p<0.001), and a perfect agreement was observed between DUS and CTA results which were again statistically significant according to ROC curve analysis (p<0.001) (Figure 3, Table 3).

Two patients who were diagnosed with type 2 endoleak on DUS were also diagnosed with type 2 endoleak on CTA. On the other hand, two of 28 cases who were not thought to have type 2 endoleak on DUS were defined as type 2 endoleak on CTA (Table 2). The Kappa coefficient calculated for the positive and negative values for the diagnosis of type 2 endoleak was found to be 0.634 (p<0.001), and there was a significant agreement between DUS and CTA results, indicating a statistical significance according to the ROC curve analysis (p<0.001) (Figure 3, Table 3).

The largest transverse diameter was measured from outer side to outer side in both DUS and CTA. There was a positive and very strong linear relationship between the two measurements (r=0.988 p=0.001) (Figure 4). The mean difference between the measurements of DUS and CTA was found to be 2.47±2.16 mm which was statistically significant

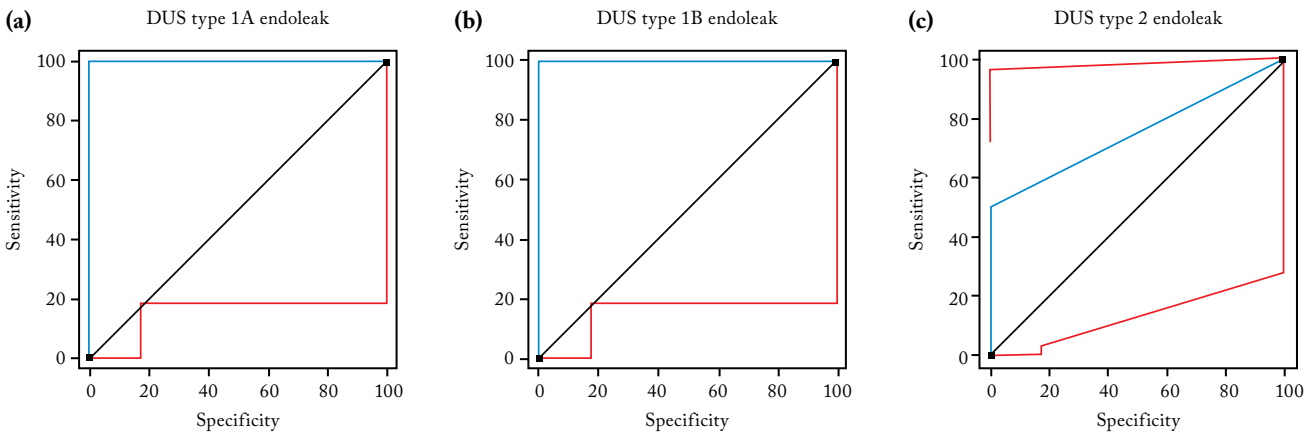

Figure 3. ROC curve analyses of DUS diagnosis according to endoleak subtypes. **(a)** Type 1A endoleak diagnosis ROC curve area under curve was calculated as 1,000 (95% CI: 0.884-1,000). **(b)** Type 1B endoleak diagnosis ROC curve area under curve was calculated as 1,000 (95% CI: 0.884-1,000). **(c)** Type 2 endoleak diagnosis the area under the ROC curve was calculated as 0.750 (95% CI: 0.559-0.889).

ROC: Receiver operating characteristics; DUS: Doppler ultrasonography; CI: Confidence interval.

Table 3
Statistical analysis of DUS according to endoleak subtype diagnosis

	Type 1A endoleak	Type 1B endoleak	Type 2 endoleak
Sensitivity	100.0	100.0	50.0
Specificity	100.0	100.0	100.0

DUS: Doppler ultrasonography.

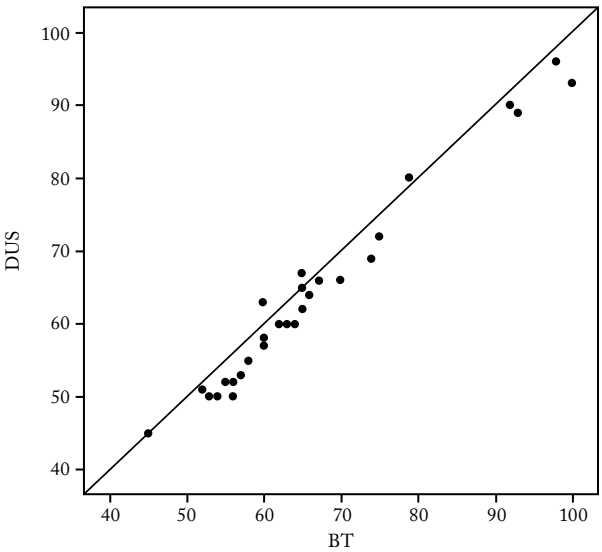

Figure 4. Comparison of aneurysm transverse diameters measured in DUS and CTA.

DUS: Doppler ultrasonography; CTA: Computed tomography angiography; CTA: Computed tomography angiography.

(p=0.001). The lower limit of the 95% confidence interval (CI) for the difference of the two measurements was 1.66 mm and the upper limit as 3.27 mm.

The endoleak types detected in the study and the secondary interventions applied after the diagnosis are summarized in Table 4. In two patients, an endoleak developed from the proximal end of the stent in the early postoperative period (Figure 5). After an additional stent replacement proximal to the stent, no endoleak was detected during follow-up. In another patient, at 12 months of the operation, symptoms developed and DUS detected a leak at the proximal end of the stent and CTA proved the leakage. An additional stent was placed at the proximal end of the stent; however, the leak continued and the patient was switched to open surgery (Figure 6). Two patients (No. 4 and No. 5) had type 2 endoleak, which was detected to originate from the lumbar arteries at the first month of control. No additional intervention was considered

Table 4
Endoleak subtypes and further interventions

Patient	Age	Sex	Endoleak subtype	Secondary intervention
1	78	M	Type 1A	An extension was placed proximal to the stent.
2	85	M	Type 1A	An extension was placed proximal to the stent.
3	76	M	Type 1A	An extension was placed proximal to the stent. Open surgery was performed after the leakage.
4	80	M	Type 2	-
5	62	M	Type 2	-
6	82	F	Type 1B	-

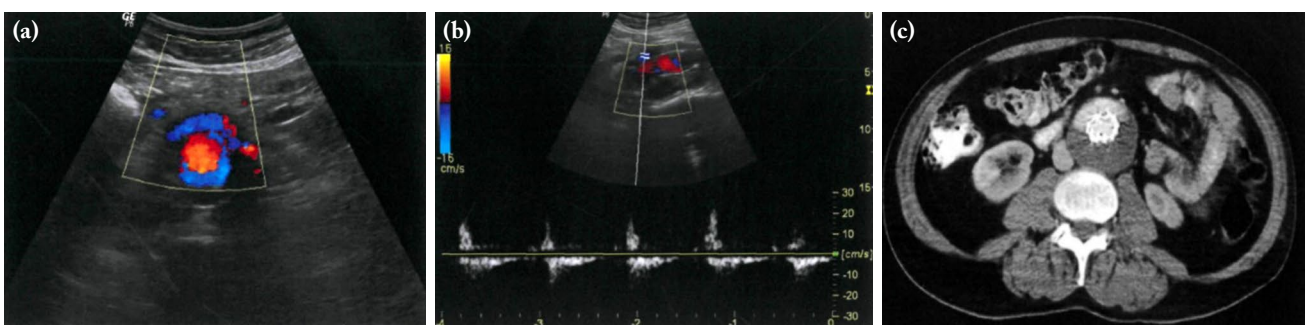

Figure 5. A 78-year-old male patient (No. 1) with endoleak development after operation. **(a)** Transverse plane DUS demonstrates type 1A endoleak on the proximal end of the graft with perigraft flow. **(b)** Arterial flow samples were detected with spectral analysis of perigraft flow. **(c)** In axial CTA images abnormal contrast filling is monitored anterior of the graft compatible with type 1A endoleak.

DUS: Doppler ultrasonography; CTA: Computed tomography angiography.

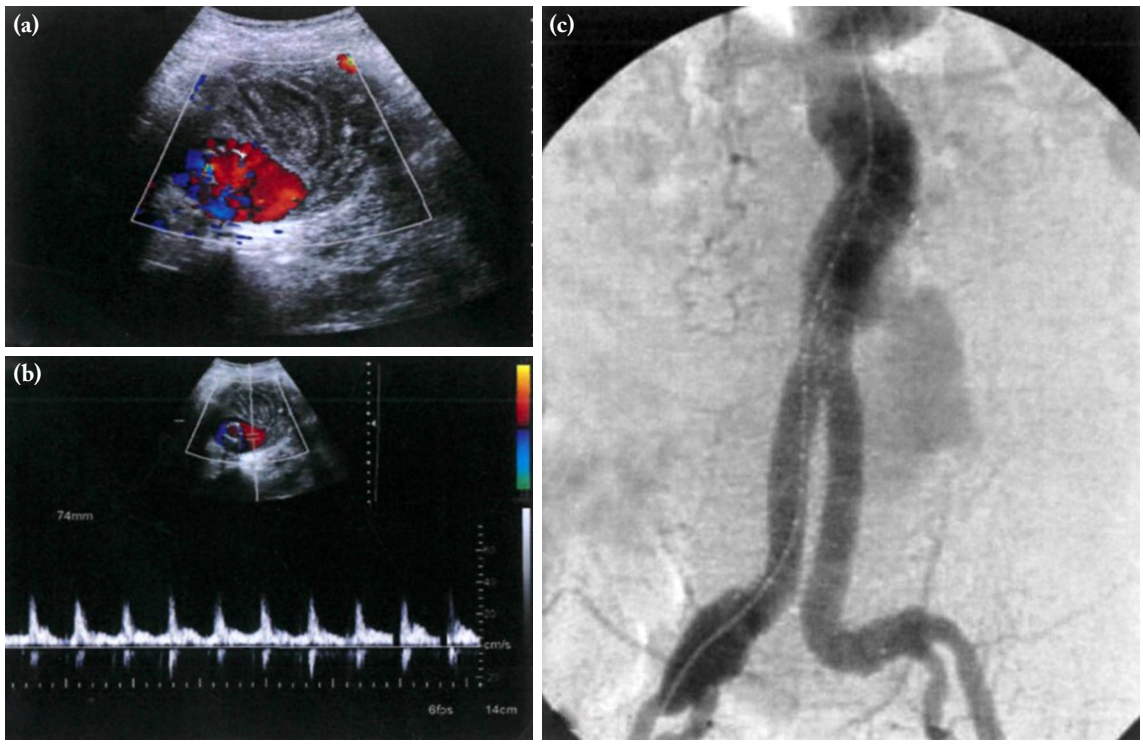

Figure 6. A 76-year-old male patient (No. 3) with type 1A endoleak development after surgery **(a)** Axial plane DUS showed color coding on proximal attachment side of graft towards to the sac. **(b)** Arterial flow pattern was detected in spectral analysis. **(c)** Preoperative CTA image showing contrast filling excess in the left proximal part of graft extending into the sac.

DUS: Doppler ultrasonography; CTA: Computed tomography angiography.

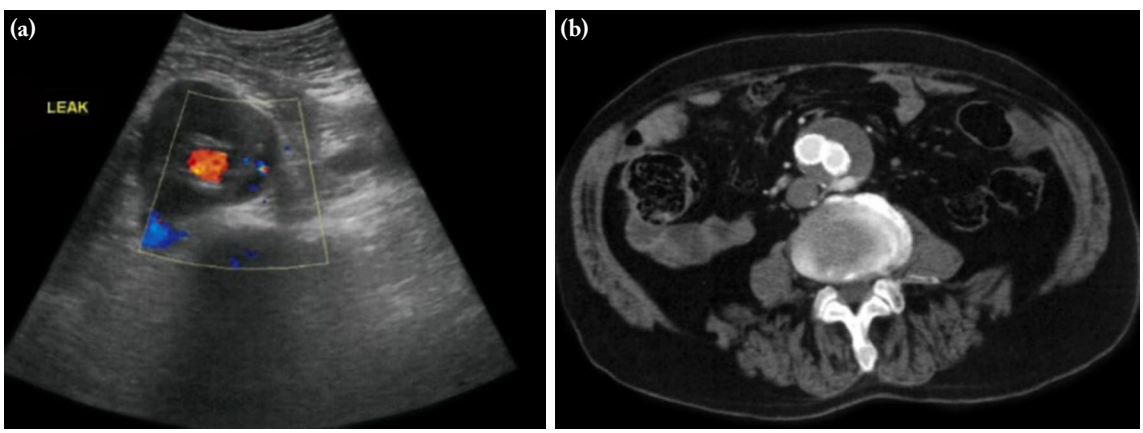

Figure 7. A 80-year-old male patient with type 2 endoleak (No. 4). **(a)** Axial DUS image demonstrating color coding at the posterior periphery of the sac. **(b)** Axial CTA image showing contrast filling compatible with type 2 endoleak from the lumbar artery.

DUS: Doppler ultrasonography; CTA: Computed tomography angiography.

in these two cases in whom shrinkage was detected in the aneurysm sac and persistence of the endoleak during follow-up (Figure 7). In another case (No. 6), the presence of flow from the graft distal attachment region into the pouch was detected consistent with type 1b endoleak at the first month of follow-up (Figure 8). Follow-up examinations showed that the leak persisted. In this case, no additional

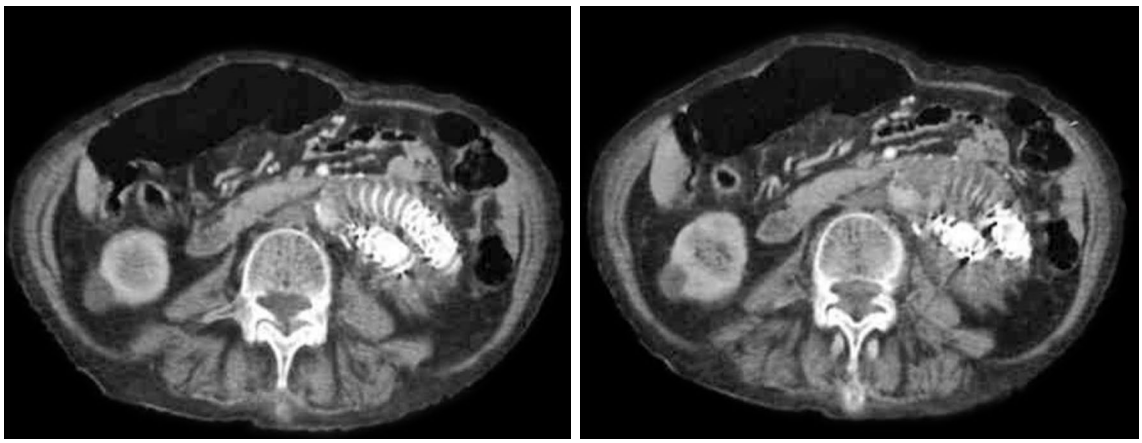

Figure 8. Sequential CTA images obtained in the axial plane showing contrast filling close to the distal part of graft consistent with type 1B endoleak (No. 6).
CTA: Computed tomography angiography.

intervention was performed due to the detection of reduction in the sac diameter, either.

DISCUSSION

Considering CTA as the gold standard, DUS was found to have a sensitivity and specificity of 75% and 100%, respectively for endoleak detection in the current study. For detecting type 1 endoleak, DUS demonstrated a sensitivity and specificity of 100% and 100%, respectively and it had a sensitivity of 50% and specificity of 100% for type 2 endoleak detection.

Persistent type 1 and 3 endoleaks may cause an increase in the pressure in the aneurysm sac, leading to enlargement of the aneurysm; therefore, rupture and death may occur. Type 2 endoleak occurs as a result of retrograde flow from patent side branches to the aneurysm sac and is considered as a low pressure endoleak.[15] Therefore, after repair with EVAR, follow-up should be done at 1, 6, and 12 months and annually thereafter up to five years according to risk status of endoleaks.[16] The CTA is the gold-standard imaging method with a short examination duration, minimal patient dependence, and three-dimensional reformat image advantages. However, it requires ionizing radiation and potentially nephrotoxic and allergic contrast agents.[17] Doppler US is a potentially alternative imaging modality to CTA. It has advantages such as not having ionizing radiation, not requiring the use of nephrotoxic and allergic contrast agents, being relatively inexpensive, non-invasive, and reproducible. However, it is a user-dependent method and has technical limitations in cases with obesity and meteorism.[18]

Studies comparing CTA and DUS in the diagnosis of post-repair endoleak with EVAR demonstrated the sensitivity of DUS to be between 25 and 100%.[16] The effectiveness of DUS varies according to the device, user experience, and endoleak types detected in the study groups. In our study, CTA was superior to DUS in the detection of type 2 endoleaks. On the other hand, no superiority was demonstrated in the detection of type 1 endoleaks. Overall, specificity of DUS to detect all subtypes of endoleaks was found to be 100%, sensitivity for type 1A and type 1B were 100%, sensitivity for type 2 was 50% in the current study. A previous study showed that DUS had a sensitivity and specificity of 74% and 94%, respectively in which they concluded that DUS could detect type 1 and 3 endoleak after EVAR.[19] In our study, the sensitivity was relatively low and the specificity was higher, considering the high level of the devices we used, indicating that it is needed to gain experience in detecting type 2 endoleaks.

The effectiveness of DUS varies according to the endoleak types detected in the study groups with different results. A study showed a sensitivity and specificity of 100% for endoleak detection with DUS, while DUS was concluded to even be superior to CTA in endoleak detection.[20] On the other hand, AbuRahma et al.[17] reported that DUS is more sensitive in detecting type 1 endoleaks than type 2 endoleaks (88% and 50%, respectively) and that DUS

had a low sensitivity, particularly in detecting type 2 endoleaks and should not be used alone. However, they also mentioned that most of the type 2 endoleaks regressed spontaneously and the intervention decisions of these patients should be determined according to the aneurysm diameter increase. In our study, the presence of type 2 endoleak, which could not be detected in DUS in two cases, was revealed by CTA. No progression or spontaneous thrombosis was detected in these patients, and after the endoleak detection, DUS follow-up was appropriate and performing CTA did not have any additional contribution. Doppler US can be used in follow-up owing to its high sensitivity and NPV compared to CTA; however, more aggressive invasive diagnostic methods can be applied when endoleak is suspected. Furthermore, low sensitivity of DUS for detecting type 2 endoleaks is acceptable, since undetected endoleaks are clinically insignificant.[21]

The increase in the aneurysm diameter is critical for intervention decision in cases with type 2 endoleak. Doppler US is a method that can be used in aneurysm diameter follow-up. Raman et al.[22] reported that CTA and DUS showed a high correlation for aneurysm diameter follow-up. Besides, it has been proposed that, although DUS is a method that can be used in the diagnosis of endoleak thanks to its high sensitivity and specificity, it gives very different results with CTA in the follow-up of aneurysm diameter.[23] Ultrasound may underestimate aortic size compared to CTA with the inner-to-inner measurement method.[24] In our study, anteroposterior and transverse diameters were measured at the widest level of the aneurysm which showed a correlation between the two measurements. However, the aneurysm diameter was measured smaller with DUS than with CTA. This difference should be kept in mind while using DUS for aneurysm diameter monitoring. In the current study, CTA measurements were made on reformat images, taking into account the tortuosity of the aorta, in the transverse plane, at its widest point, and from outer to outer.

AbuRahma et al.[17] reported that, apart from the known limitations of DUS, it was not exactly known how the stent graft could affect the sound conduction as a factor that might cause errors in the detection of endoleaks. The decrease in the transmission of sound waves by the stent may cause the sensitivity of DUS to decrease in endoleak detection. In our study, color artifacts behind the graft during DUS examination were also problematic. Similar to mirror artifact behind the stent, pulsating artifacts such as color coding of the flow in the stent may occur. To distinguish it from true endoleak, it was examined from different angles. The location of the true endoleak remains constant, while the artifacts change their location and are always seen behind the stent, enabling the distinction between endoleak and artifact.

In their study, Berdejo et al.[25] reported that DUS might be an effective technique for the postoperative evaluation of patients treated with endovascular grafts and might be the main diagnostic method in the post-intervention follow-up in the near future. According to their own experience, false negative results depended on suboptimal examinations or the examination technique. They also emphasized that it was necessary to know the underlying pathology and the details of the procedure performed in each patient. Bargellini et al.[26] compared the results of CTA and DUS in 196 patients after EVAR and showed that DUS was a method that could be used alone after the first-year follow-up after repair with EVAR, bearing in mind the low diagnostic value in aneurysm diameter measurements, and CTA should be used in cases with persistent diameter increase. In our study, CTA and DUS results were correlated, suggesting that DUS is an alternative method to CTA in the diagnosis of endoleak. Unlike the previous study, the current study demonstrates that DUS can be a method that can be used in the aneurysm diameter follow-up.

Through the evaluation of the hemodynamics of the artery with pulse wave DUS, waveforms or measuring current velocities for type 2 endoleak persistency can be detected.[27] Therefore, it can be speculated that DUS, with the help of hemodynamic parameters, can contribute to the determination of the prognosis and prevention of more serious complications. In our study, the possibility of thrombosis was not evaluated by comparing intra-endoleak flow velocity measurements or evaluating waveforms. The presence of arterial flow in the aneurysm was investigated and after the endoleak was detected, the vascular structure that could be the source was determined.

Several studies have also been conducted on the use of contrast media in post-repair ultrasonographic examination with EVAR. While there are studies that argue that contrast-enhanced US is not a reliable method in the follow-up after repair with EVAR, there are also studies suggesting that it can detect endoleaks even that CTA cannot detect.[28] In the current study, unfortunately, we were unable to use

contrast agents during DUS and could not compare the further results.

The main limitations of the present study include its single-center, retrospective design with a relatively small sample size. In addition, follow-up period was short and optimal time point for follow-up could not be achieved, and pulse wave measurements were not available.

In conclusion, DUS is potentially an alternative imaging modality to CTA, although it has low sensitivity for detecting type 2 endoleaks during post-repair follow-up after EVAR. It has many advantages over CTA during routine follow-up. It may be appropriate to evaluate with CTA when an increase in the aneurysm diameter, graft migration or rupture is suspected. It is important to strictly adhere to the DUS examination protocol and evaluation criteria to minimize false-positive or false-negative results. As the number of cases and experience increase, it may be possible to use DUS as an alternative to CTA in the routine follow-up of all patients.

Declaration of conflicting interests

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The effect of hemodialysis on left ventricular global longitudinal strain in chronic hemodialysis patients with preserved left ventricular ejection fraction

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ABSTRACT

Objectives: In the present study, we aimed to evaluate the acute effects of hemodialysis (HD) on left ventricular functions with left ventricular (LV) global longitudinal strain (GLS).

Patients and methods: This prospective study included a total of 38 patients (24 males, 14 females; mean age: 60.8±13.8 years; range, 31 to 82 years) who were on chronic HD for at least six months and had a LV ejection fraction of ≥50% between December 2021 and January 2022. The clinical and echocardiographic features of the patients were recorded before and after HD. The GLS was calculated using two-dimensional speckle-tracking method.

Results: The mean dialysis time of the patients was 6.3±3.9 years. The left atrial volume index was significantly lower after HD than before (30.1±10.0 *vs.* 27.5±8.2 mL/m^2, p=0.005). Pulsed Doppler echocardiography showed significantly decreased E and A wave peak velocity after HD (99.3±38.2 *vs.* 80.4±27.8 cm/s, p=0.001 and 99.4±23.2 *vs.* 90.4±25.5 cm/s, p=0.022), but no significant change in the E/A ratio (1.1±0.5 *vs.* 1±0.6, p=0.660). There was no significant change on the LV GLS between before and after HD (-17.3±2.6 *vs.* -16.9±2.6%, p=0.088).

Conclusion: Hemodialysis has no significant effect on LV GLS in the acute phase in patients with end-stage chronic renal disease.

Keywords: End-stage renal disease, global longitudinal strain, hemodialysis, speckle-tracking echocardiography.

Cardiac morbidity and mortality are higher in patients with end-stage renal disease (ESRD) than in the normal population.[1] Structural and functional cardiac changes can be observed in ESRD patients undergoing hemodialysis (HD) due to causes such as chronic volume and pressure overload, anemia, uremia, high-flow arteriovenous shunts, abnormal calcium and phosphate metabolism, and hyperparathyroidism.[2,3] In addition, rapid blood volume and electrolyte changes during HD may cause acute deterioration in cardiac functions. Cardiac functions in HD patients have been extensively studied by conventional echocardiography; however, this method offers only a semiquantitative assessment and cannot detect subclinical cardiac dysfunctions.

Despite a high prevalence of cardiovascular insults and progressive symptoms of heart failure, left ventricular ejection fraction (LVEF) remains preserved in the majority of patients with chronic kidney disease (CKD).[4] Speckle-tracking echocardiography with myocardial deformation (two-dimensional [2D] strain) analysis is a quantitative method for the assessment of subtle left ventricular (LV) dysfunction, which cannot be evaluated by semiquantitative conventional echocardiography.[5] Left ventricular global longitudinal strain (GLS) has been proposed to be a new indicator of systolic function. However, using speckle-tracking echocardiography to assess acute effects of HD on cardiac function has resulted in contradictory results.[6] Although some studies have reported that HD improves cardiac functions in the acute period, others have shown that it affects them negatively.[7-10] In the current study, we aimed to investigate the acute effect of HD on LV GLS in chronic HD patients with preserved LVEF.

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PATIENTS AND METHODS

This single-center, prospective study was conducted at Izmir Bakırçay University, Department of Cardiology between December 2021 and January 2022. A total of 38 patients (24 males, 14 females; mean age: 60.8±13.8 years; range, 31 to 82 years) who were on chronic HD for at least six months and had an LVEF of ≥50% were included. Exclusion criteria were as follows: age <18 years, LVEF <50%, undergoing acute HD, presenting with the acute coronary syndrome and/or pulmonary edema within the last one month, presence of cardiac resynchronization therapy, and inadequate echocardiography imaging quality. A written informed consent was obtained from each patient. The study protocol was approved by the Bakırcay University Non-interventional Clinical Research Ethics Committee (Approval number: 2021/471). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Echocardiography was performed immediately before and immediately after HD in all patients included in the study. Two-dimensional conventional and speckle-tracking echocardiography data of the patients were recorded. Clinical information on comorbidities, medical history, and current cardiovascular medication was obtained by careful review of each patient's medical record and a self-reported questionnaire. All patients were assured to receive adequate clearance by dialysis. The blood pressure and pulse rate values of the patients were recorded before and after HD. The patients were weighed before and after HD and their body weights were recorded. Hemodialysis times, ultrafiltration volumes, and rates of all patients were noted. Baseline blood values taken before the HD session at the beginning of the week were recorded. The body mass index (BMI) of the patients was calculated with the formula: body weight/height in meters squared.

Echocardiography

The Philips EPIQ echocardiography instrument (EPIQ 7, Philips Medical Systems, USA) with a X5-1 probe (Q-lab digital software version 10) was used together with a Q-Lab digital software (Philips Medical Systems, USA) for offline analysis. All echocardiographic parameters were measured offline in batches by two experienced cardiologists blinded to clinical and outcome data. Echocardiography was performed immediately before and immediately after HD.

Two-dimensional echocardiography

Left ventricular ejection fraction was assessed using the biplane Simpson's method from apical four- and two-chamber views. Preserved LVEF was defined as ≥50%. Left ventricular diastolic and systolic diameters were measured from the parasternal long axis view. Peak early (E) and late (A) diastolic velocities of the mitral inflow were evaluated by pulse wave Doppler. Tricuspid regurgitation velocity (TRV) and right atrial pressure were used to estimate pulmonary artery systolic pressure (PASP). Left atrial volume index (LAVI) was measured using the biplane area length method and was indexed to body surface area.

Two-dimensional speckle-tracking echocardiography

Apical four-, three-, and two-chamber views were acquired with high frame rate (>50 fps) for 2D speckle-tracking strain analysis. Offline analyses were performed using Automated Cardiac Motion Quantification software on Q-lab version 10 (Philips Medical Systems, USA). To define the region of interest, the endocardial surface was identified by manually placing at least 15 markings in all apical views. Systolic longitudinal strain was automatically obtained from the three standard apical views (Figure 1). The average systolic longitudinal strain value from the three apical views was regarded as the GLS (Figure 2).

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 15.0 software (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to check for normality of distribution for continuous variables. Continuous variables were presented in mean ± standard deviation (SD) or median (min-max), while categorical variables were presented in number and frequency. Paired samples t-test was used to compare continuous variables before and after HD. Categorical variables were compared using the Pearson chi-square and Fisher exact test. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 38 patients included in the study, 33 (86.8%) had hypertension, 13 (34.2%) had diabetes

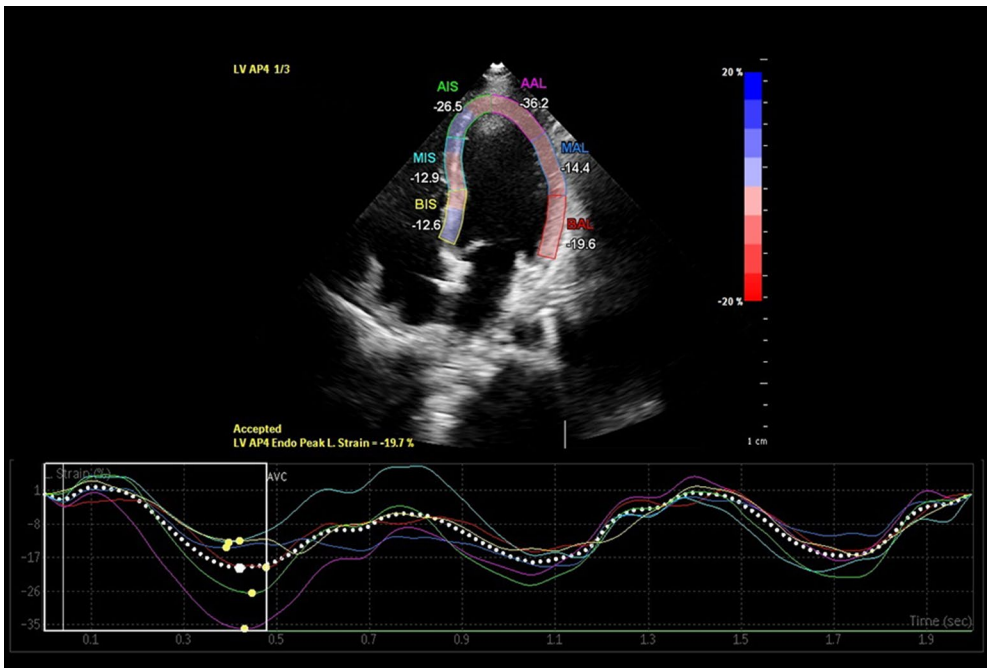

Figure 1. Two-dimensional speckle-tracking echocardiography for left ventricular 4-chamber longitudinal strain.

mellitus, and 14 (36.8%) had coronary artery disease. The mean HD time of the patients was 6.3±3.9 years. The mean ultrafiltration volume of the patients during HD was 2,428±847 mL. Seventeen of the patients were using an antiaggregant agent and two were using an oral anticoagulant. Of the patients, 26 (68.4%) were using vitamin D and 32 (84.2%) were using erythropoietin. Baseline demographic and medication features of the patients are presented in Table I and laboratory findings are presented in Table II.

While there was no significant difference in the mean heart rate before and after HD (73.1±8.6 *vs.* 74.5±8.9 bpm, p=0.194), mean systolic and diastolic

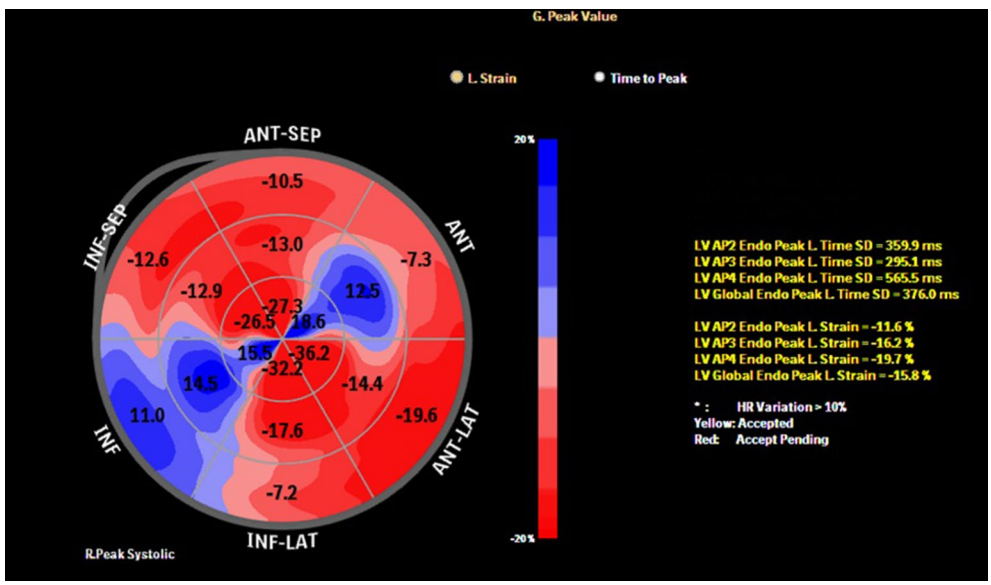

Figure 2. The average left ventricular global longitudinal strain (bull's eye plot).

Table 1
Baseline characteristics of the patients (n=38)

Variables	n	%	Mean±SD
Demographic			
Age (year)			60.8±13.8
Sex			
Male	24	63.2	
Diabetes mellitus	13	34.2	
Hypertension	33	86.8	
Hypercholesterolemia	7	18.4	
Coronary artery disease	14	36.8	
COPD	6	15.8	
Peripheral vascular disease	5	13.2	
Cerebrovascular disease	2	5.3	
Hemodialysis and ultrafiltration			
Duration of HD (year)			6.3±3.9
Ultra-filtrated volume (mL)			2428±847
Medication			
Acetylsalicylic acid	12	31.6	
ADP receptor inhibitors	5	13.2	
Oral anticoagulants	3	7.9	
Beta-blockers	12	31.6	
Calcium-channel blockers	5	13.2	
ACE-i/ARB	1	2.6	
Statin	4	10.5	
Loop diuretics	11	28.9	
Oral antidiabetic	3	7.9	
Insulin	10	26.3	
Anti-potassium	1	2.6	
Anti-acidosis	3	7.9	
Vitamin D	26	68.4	
Erythropoietin	32	84.2	

SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; HD: Hemodialysis; ADP: Adenosine-diphosphate; ACE-i: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II-receptor blocker.

Table 2
Laboratory characteristics of the patients (n=38)

Variables	Mean±SD
Fasting blood glucose (mg/dL)	128.1±48.2
Urea (mg/dL)	120.8±35.3
Creatinine (mg/dL)	8.2±2.2
Uric acid (mg/dL)	5.5±1.1
Sodium (mEq/L)	138.1±3.1
Potassium (mg/dL)	4.9±0.6
Calcium (mg/dL)	8.9±0.6
Phosphorus (mg/dL)	4.7±1.4
Ferritin (ml/ng)	525.4±548.4
TSH (mU)	2.3±1.3
Parathormone (pg/mL	520.7±733.5
Total cholesterol (mg/dL)	162.2±39.2
HDL-cholesterol (mg/dL)	38.8±11.1
LDL-cholesterol (mg/dL)	95.8±34.1
Plasma triglycerides (mg/dL)	136.5±67.3
White blood cell count ($\times 10^9$ /L)	6.5±1.8
Hemoglobin (g/dL)	10.5±1.5
Hematocrit (%)	32.5±4.4
Platelet count (10^9 /L)	220.8±68.4

SD: Standard deviation; TSH: Thyroid stimulating hormone; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

blood pressures were significantly lower after HD (136.1±29.1 *vs.* 111.9±20.6 mmHg, p<0.001 and 77.1±14.7 *vs.* 69±12.8 mmHg, p<0.001, respectively). The clinical parameters of the patients before and after HD are presented in Table III.

Of the echocardiographic parameters, the mean LV end-diastolic volume and end-systolic volume were significantly decreased after HD (97.02±20.19 *vs.*

Table 3
Clinical parameters before and after hemodialysis

	Before HD	After HD	
Variables	Mean±SD	Mean±SD	*p*
Systolic blood pressure (mmHg)	136.1±29.1	111.9±20.6	<0.001
Diastolic blood pressure (mmHg)	77.1±14.7	69±12.8	<0.001
Heart rate (bpm)	73.1±8.6	74.5±8.9	0.194
Weight (kg)	74.3±18.4	72.2±18.2	<0.001
Body mass index (kg/m^2)	27.2±7.5	26.4±7.4	<0.001

HD: Hemodialysis; SD: Standard deviation.

Table 4
Echocardiographic parameters before and after hemodialysis

Variables	Before HD Mean±SD	After HD Mean±SD	*p*
LV end-diastolic internal diameter (cm)	47.7±3.8	47.1±3.3	0.081
LV end-systolic internal diameter (cm)	28.9±3.3	28.5±2.9	0.058
LV end-diastolic volume (mL)	97.0±20.2	92.0±17.9	0.002
LV end-systolic volume (mL)	40.1±11.1	37.9±10.5	0.008
LV ejection fraction (%)	59.6±4.1	59.4±3.9	0.208
PASP (mmHg)	23.5±7.4	23.1±6.0	0.286
LA area (4-chamber view) (cm^2)	17.7±4.5	16.5±3.5	0.001
LA volume (mL)	54.7±17.1	49.7±15.5	0.002
LA volume index (mL/m^2)	30.1±10.0	27.5±8.2	0.005
E (cm/s)	99.3±38.2	80.4±27.8	0.001
A (cm/s)	99.4±23.2	90.4±25.5	0.022
E/A	1.1±0.5	1±0.6	0.660
LV GLS (%)	-17.3±2.6	-16.9±2.6	0.088

HD: Hemodialysis; SD: Standard deviation; LV: Left ventricle; PASP: Pulmonary artery systolic pressure; LA: Left atrium; E: Peak early diastolic trans-mitral flow velocity; A: Peak late diastolic trans-mitral flow velocity; GLS: Global longitudinal strain.

92.0±17.9 mL, p=0.002 and 40.1±11.1 *vs.* 37.9±10.5 mL, p=0.008, respectively). Similarly, left atrial area, left atrial volume, and LAVI were significantly lower after HD than before (17.7±4.5 *vs.* 16.5±3.5 cm^2, p=0.001, 54.7±17.1 *vs.* 49.7±15.5 mL, p=0.002, and 30.1±10.0 *vs.* 27.5±8.2 mL/m^2, p=0.005, respectively). Pulsed Doppler echocardiography showed significantly decreased E and A wave peak velocity (99.3±38.2 *vs.* 80.4±27.8 cm/s, p=0.001 and 99.4±23.2 *vs.* 90.4±25.5 cm/s, p=0.022), but no significant change in the E/A ratio (1.1±0.5 *vs.* 1±0.6, p=0.660). There was no significant change on the LV GLS between before and after HD (-17.3±2.6% *vs.* -16.9±2.6%, p=0.088). The echocardiographic parameters of the patients are presented in Table IV.

DISCUSSION

The present study showed that HD did not significantly affect LV GLS, LVEF, and E/A ratio in the acute phase in patients with chronic ESRD.

Chronic kidney disease is a unique risk factor for cardiac remodeling. An experiment in mice showed that early subendocardial changes were worse in those with CKD than in those without.[11] The LVEF measures predominantly radial contraction, while GLS represents the function of subendocardial longitudinal myocardial fibers, which are more sensitive to decreased coronary perfusion and increased wall stress.[12,13] The GLS reflects the longitudinal contraction of the myocardium and its accuracy has been validated against tagged magnetic resonance imaging.[14] The GLS not only provides a quantitative assessment of myocardial function, but also reflects changes in the myocardial interstitium, including myocardial fibrosis.[15] Compared to the general population, the incidence of cardiovascular death in HD patients is 10 to 20 times higher.[1,16] In the general population, GLS was shown to be a superior predictor of cardiac events and all-cause mortality compared to LVEF.[17] Kramann et al.[15] showed that strain parameters were independent risk factors for cardiovascular and all-cause mortality.

Many previous studies have reported that HD adversely affects LV GLS and LVEF.[7,18,19] Indeed, LV functions are expected to improve after HD due to reduced preload and afterload, but there are different mechanisms that affect LV GLS. In addition, hemodynamic changes experienced during HD may worsen LV function by causing myocardial ischemia, myocardial damage or stunning. In a study conducted by Unlu et al.,[9] troponin-T increased with the decline

of GLS after HD. In contrast, Liu et al.[10] found that patients with ESRD who received HD had better LV GLS than those who did not. It was stated that the reason for this was the elimination of the negative effects of renal failure on LV functions by HD.

In some studies similar to our study results, it has been shown that HD does not have a significant effect on LV systolic functions.[20,21] In a different study, Amoozgar et al.[22] found no notable change in LV GLS after HD in children receiving HD, and believed that children's LV GLS was preload independent. The most important cause of deterioration in LV functions during HD is rapid intravascular volume changes. Other possible causes that increase this deterioration are changes in ionized calcium concentration, sympathetic hyperactivity, increased oxidative stress during HD, and low-resistant vessels. In our study, the mean dialysis time was 4 h and controlled ultrafiltration was performed without causing sudden hypotension. This is the most important reason why there was no significant change in LV GLS before and after HD in our study.

In the current study, a decrease in left atrial and ventricular volumes, which are indicators of preload, was found after HD, similar to the findings of Wang et al.[7] However, there was no significant change in LVEF. Furthermore, we found that HD-associated volume reduction changed mitral valve inflow parameters. Both E-wave and A-wave decreased significantly after HD, but there was no significant decrease in E/A ratio. The E/A ratio is an important indicator of LV filling and diastolic function. There was no significant change in the E/A ratio reflecting diastolic functions after HD, just as in LV GLS reflecting systolic functions.

This study has some limitations. The study has a single-center design with a relatively small sample size, and its results need to be further confirmed by a more rigorous and large-sample prospective study. In addition, LV GLS changes after HD according to the ultrafiltration volumes of the patients were not examined separately, which may have affected the LV GLS results.

In conclusion, HD has no significant effect on LV systolic and diastolic functions in the acute phase in patients with chronic ESRD. Avoiding rapid blood volume changes with controlled ultrafiltration during HD may prevent deterioration of LV functions.

Declaration of conflicting interests

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Early clinical results of surgical treatment of active infective endocarditis

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ABSTRACT

Objectives: In this study, we present early results of surgery in patients who were surgically treated for active infective endocarditis (IE).

Patients and methods: Between October 2015 and June 2020, a total of 28 patients (21 males, 7 females; mean age: 62±9 years; range: 46 to 78 years) with an active IE who were not previously operated were retrospectively analyzed. The diagnosis of IE was made on the basis of clinical and transthoracic echocardiographic findings, and microbiological growth in the blood culture. The patients were divided into two groups according to the type of surgery [Group 1 (valve replacement group; n=21) and Group 2 (valve repair; n=7)]. Baseline and operative data of the patients were compared.

Results: The median follow-up was 3.4 (range: 2-5 yeras) years. Blood cultures were positive in 19 (67.8%) patients. Coagulase-negative *Staphylococci*, *Staphylococcus epidermidis*, and methicillin-resistant *Staphylococcus aureus* were the most common microorganisms. The main symptoms were fever, fatigue, shortening of breath, and dyspnea. We performed an urgent surgery in six patients who had congestive heart failure resistant to medical treatment (n=2) and pulmonary embolic events (n=4). If there were perivalvular abscess formation, and multiloculated mobile and large vegetations in patients with sepsis or hemodynamic instability despite intense medical treatment including inotropic administration, we preferred early surgery. The postoperative mortality rate was 10.7%.

Conclusion: Our study results suggest that active IE is associated with high mortality rates. Valve repair may be chosen in eligible patients after the extensive resection of infected leaflets with acceptable results.

Keywords: Complications, heart failure, infective endocarditis, medical treatment, surgery.

Active infective endocarditis (IE) is a rare, but severe clinical condition.[1-3] Despite advancements in early diagnosis, new medical treatments, comprehensive antibiotics regimens, and accumulated experiences with surgical approaches, it is still associated with a high mortality rate. The main risk factors are congenital heart diseases, previous cardiac surgery, degenerative valvular disease, central venous catheter insertion, and placement of a pacemaker or implantable cardioverter defibrillator (ICD), and intravenous drug use (IVDU).[4-10]

The treatment of IE and the optimal timing of surgery have been described by the European Association for Cardiothoracic Surgery (EACTS),[7] American College of Cardiology (ACC)/American Heart Association (AHA),[8] and the Turkish Society of Cardiovascular Surgery and Turkish Society of Thoracic Surgery (TSCVS).[9,10] To prevent high morbidity and mortality in patients with heart failure, or mobile and large vegetations, as well as in patients with recurrent embolic events, early surgery has been proposed.[9,10] Early surgery has also been suggested in patients with periannular abscess formation, serious valvular stenosis or valvular regurgitation related to multiple vegetations, and septic embolic events.[9,10] In addition, the guidelines of the EACTS[7] AHA,[8] and TSCVS[9,10] suggest an early surgery as evidence of Class IIb in patients with a vegetation size of >15 mm.

About a quarter of the patients can be treated using antibiotics without requiring a surgical intervention.[11] In a multi-center study, Oylumlu et al.[11] reported the clinical results of 116 patients with IE who underwent medical treatment and surgery. They recommended surgery in 53% of patients who had severe valvular destruction. In this series, the mortality rate was 19.5%. The predictors of mortality were higher New York Heart Association (NYHA)

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functional class, elevated C-reactive protein, and renal dysfunction.

In the present study, we report early clinical results of surgical treatment of IE after valvular replacement and repair.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Elazığ Fethi Sekin Eğitim ve Araştırma hastanesi, Department of Cardiovascular Surgery between October 2015 and June 2020. A total of 28 patients (21 males, 7 females; mean age: 62±9 years; range: 46 to 78 years) with an active IE for the first time. The diagnosis of IE was made on the basis of clinical and echocardiographic findings, and microbiological growth in the blood culture.[12] The patients were divided into two groups according to the surgical approach as Group 1 (n=21; valve replacement group) and Group 2 (n=7; valve repair group). Written informed consent was obtained from each patient. The study protocol was approved by the Elazığ Fethi Sekin Research and Training Hospital Ethics Committee (No: 903.05.99-399). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Surgical pproach

After the induction of anesthesia, the transesophageal echocardiography (TEE) probe was inserted in the appropriate position. After a median sternotomy, aorto-bicaval cannulation was performed, and an extracorporeal circulation (ECC) was instituted. We used moderate hypothermia in all operations. Cardiac arrest was achieved by the antegrade aortic route with cold blood cardioplegia.

The aim of our surgical strategy was based on *(i)* intensive debridement of the infected area followed by vegetectomy, *(ii)* whenever possible, we performed valve repair with the use of bioprosthetic materials, *(iii)* if the patients had severe destruction of the valves, we performed cardiac valve replacement using a biological substitute without the use of any artificial materials. Since the majority of patients were older than 60 years, we preferred bioprosthetic valve implantation. If the patient had no severe destruction of valves' leaflets with small size vegetation and if there was no evidence of periannular abscess formation, we used the valve repair technique. The chordal transfer was performed following the leaflet repair after the excision of the infected tissue. Leaflet excision was performed using a triangular or a quadrangular-shaped resection in an isolated mitral valve IE. We repaired the hole in the right coronary sinus of the aortic valve using fresh pericardium. If there was a periannular abscess formation, we removed the periannular tissue with the valve(s) and we repaired it using a bovine or fresh pericardium. Furthermore, we also implanted an artificial valve. In patients with a history of cardiac valve replacement, we removed all the infected materials and prosthetic valve, and we debrided the periannular tissue. We performed Kay annuloplasty or bicuspidization in patients with tricuspid valve IE. An annular ring was inserted following valvuloplasty. We replaced the pulmonary valve using a decellularized pulmonary homograft in one patient who had severe destruction of the valve accompanied by a pulmonary embolic event, followed by the extensive removal of vegetation including the pulmonary valve. Thrombectomy from the left pulmonary artery was performed. In one older patient with mitral valve IE combination, we performed coronary artery bypass grafting using the left internal thoracic artery and an artificial mitral valve was implanted.

To confirm the valve regurgitation in the repair group, TEE was performed after weaning from ECC for each patient routinely. We only observed a mild mitral valve regurgitation in two patients after repair. Broad-spectrum antibiotics were given to all patients for four to six weeks after surgery. Our postoperative antibiotic regimen included vancomycin, meropenem, and rifampicin. We discontinued rifampicin at the end of Day 10.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD), while categorical variables were expressed in number and frequency. Two-sample Student's t-test and chi-square test were used to compare the demographics of valve replacement and repair groups. All continuous variables were analyzed using the t-test. The Fisher exact test was used for categorical data. A p value of <0.05 was considered statistically significant.

RESULTS

Preoperative patients' demographics are summarized in Table 1. The mean NYHA class was 2.9±1.1. Congestive heart failure was observed in

two patients (7.1%). Pulmonary embolic events were detected using thoracic computed tomography (CT) in four patients. Two patients had an isolated right-sided IE. Left-sided IE accompanied with a right-side involvement was detected in the remaining two patients.

Fever, shortening of breath, and fatigue were the main symptoms. Severe left anterior descending artery stenosis was detected in one patient. We performed an urgent surgery on six patients due to intractable heart failure or pulmonary embolic events. We performed valve replacement or valve repair. The

Table 1
Data of patients

	Valve replacement group			Valve repair group			
	n	%	Mean±SD	n	%	Mean±SD	*p*
No of patients*	21	75		7	25		0.0001
Mean age (year)			66.1±4.7			58.6±7.4	0.66
Sex							-
Male	16			5			
Female	5			2			
Biochemical data							
Anemia	8	38		2	28.5		0.46
Leukocytosis	9	42.8		4	57.1		0.68
Thrombocytopenia*	7	33.3		2	28.2		0.010
Reasons for infective endocarditis							
Rheumatic valvular disease	11			-			
History of valve surgery	6			-			
Intravenous drug use	3			-			
Hemodialysis catheter insertion	4						
Pace-maker lead implantation	3						
ICD lead	1						
Total	28						
Preoperative TTE							
LVEF (%)			54±5			50±4	0.864
Mean PAP (mmHg)			44±21			39±17	0.720
Mean vegetation size (mm)*			44±0.9			22±0.4	0.0034
Complications of AIE							
Perivalvular abscess	2						
Intracardiac thrombus	2						
Pulmonary embolic event	4						
Congestive heart failure	2						
Duration of hospitalization (days)			53±38			49±28	0.79
NYHA functional class							
Class I	11	39.2		3	42.8		0.445
Class II	6	21.4		2	28.5		0.554
Class III	3	14.2		1	14.2		0.667
Class IV	1	4.7		1	14.2		0.023

SD: Standard deviation; ICD: Implantable cardioverter defibrillator; TTE: Transthoracic echocardiography; LVEF: Left ventricular ejection fraction; PAP: Pulmonary artery pressure; AIE: Active infective endocarditis; NYHA: New York Heart Association; * Statistical significance.

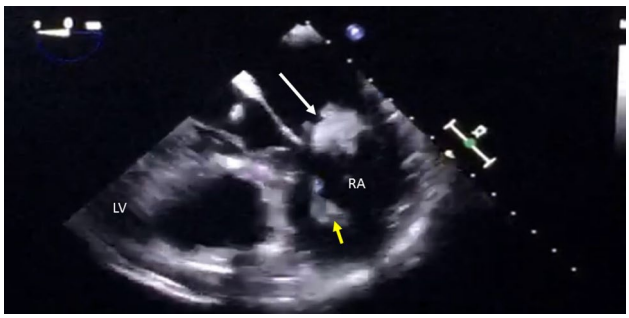

Figure 1. Transthoracic echocardiograms showing large intracardiac vegetation of tricuspid valve in a young intravenous drug abuse patient (white arrow). The vegetation is the cause of valvular stenosis. The yellow arrow shows interatrial thrombus formation.

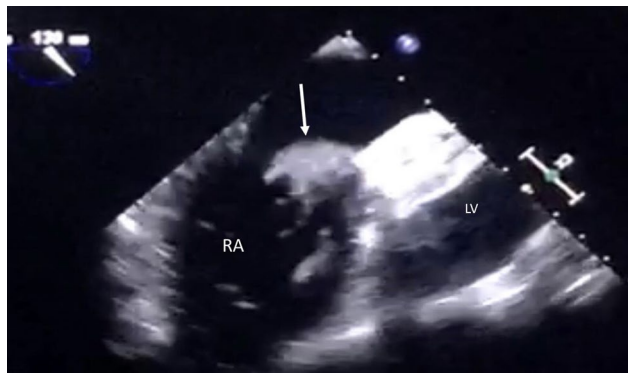

Figure 2. Transthoracic echocardiogram showing vegetation of tricuspid valve. The diameter of vegetation is 33 mm (white arrow). This patient has severe tricuspid valve regurgitation.

mean age in the replacement and repair group was similar (p=0.66).

Rheumatic valvular disease and previous cardiac valve replacement were common reasons of IE. Blood cultures were positive in 19 (67.8%) patients. Coagulase-negative *staphylococci*, *S. epidermidis*, and methicillin-resistant *Staphylococcus aureus* were the predominant agents (n=14; 50%). We used TTE as a diagnostic tool for definition of IE in all patients (Figures 1, 2, and 3).

The mean time from the diagnosis of IE to surgery was 33±12 (range, 15 to 46) days. The aortic and mitral valve were the most commonly affected valves (81%). Isolated right-sided IE was observed in four patients.

Three patients died after surgery (10.7%). Acute renal failure developed in one patient. The median length of hospitalization in the replacement and repair group were similar (p=0.76). The mean left ventricular ejection fraction (LVEF) was similar in the replacement and repair group (p=0.644). The mean duration of ECC and an aortic cross-clamp time are summarized in replacement and repair group in Table 2. The median duration of ECC and an aortic cross-clamp time in patients who underwent double valve replacement were significantly longer compared to the repair and single valve replacement group (p=0.0022 and p=0.0001, respectively). Cardiopulmonary bypass time, and ACC time in

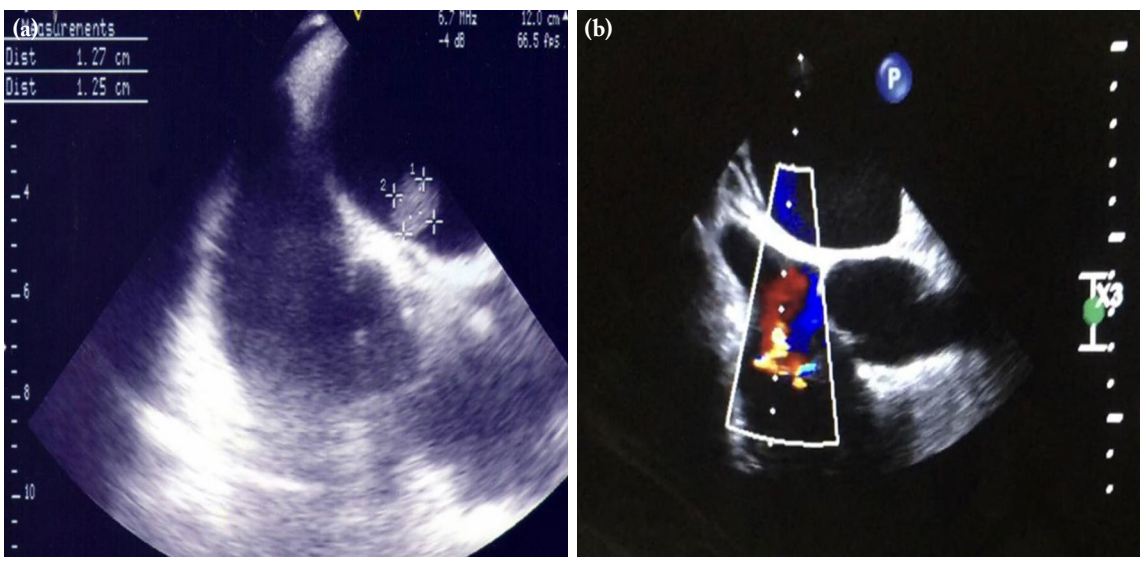

Figure 3. **(a)** Transthoracic echocardiogram showing vegetation in the subaortic region in a male patient who has a rheumatic valvular disease. **(b)** There is an aortic valvular insufficiency.

Table 2
Surgical approaches in replacement and repair groups

	Single valve replacement				Valve repair				Double valve replacement				
	n	%	Mean±SD	%	n	%	Mean±SD	%	n	%	Mean±SD	%	*p*
No of patients	11	39.2			7	25			10	47.6			0.0001
ECC time (min)			111±53				121±44				176±63		0.0026
Ao-x-clamp time (min)			76±33				83±37				124±29		0.0001
Bleeding from the mediastinum (mL)			406±55				366±80				720±160		0.0020
Vasoactive inotropic score				4.9				5.6				9.7	
Kind of surgery													
AVR	3	10.7			1*	3.5*							
MVR	4	14.2			3†	10.7†							
TVR	3	10.7			3‡	107‡							
PVR	1	3.5											
AVR+MVR									8	28.5			
MVR+TVR									3	10.7			
TEE after surgery													
Mild regurgitation					2	28.5							
Mean LVEF			52±1				49±6				53±1		0.644

SD: Standard deviation; ECC: Extracorporeal circulation; Ao-x-Clamp: aortic cross-clamp; AVR: Aortic valve replacement; MVR: Mitral valve replacement; TVR: Tricuspid valve replacement; PVR: Pulmonary valve replacement; TEE: Transesophageal echocardiography; LVEF: Left ventricular ejection fraction; * Aortic valve repair; † Mitral valve repair; ‡ Tricuspid valve repair.

the repair and single valve replacement group were similar. The mean amount of bleeding from the mediastinum was significantly higher in the double valve replacement group compared to the repair group (720±180 mL *vs.* 366±80 mL, respectively; p=0.002). Double valve replacement group received a mean of 3.1±0.9 packed red blood cells and 450±80 mL fresh frozen plasma after surgery. In the double valve replacement group, the vasoactive inotropic score was significantly higher compared to the repair and single replacement group (VIS: 9.7) (p=0.001). Transesophageal echocardiography showed that there was a mild valvular regurgitation in two patients after their valve repair.

Intubation time was longer than 24 h in two patients with congestive heart failure who underwent urgent surgery. Duration of ICU was longer in patients who underwent a double valve replacement. The duration of inotropic support was long and recovery in pulmonary function tests took time in two elderly patients. We performed hemodialysis, since two patients developed transient kidney failure. Kidney functions recovered on Day 5.

Follow-up period

The mean follow-up was 980±651 (range, 456 to 1,234) days. The survival rate after the operation was 85.8% at six months. Survival rate at the end of the first year and third year were 82.2% and 75%, respectively. The reasons for mortality were myocardial infarction, cerebrovascular accident, cancer, and congestive heart failure. We performed periodic TTE to investigate the recurrence of IE, valvular, and myocardial functions. We performed mitral valve replacement in one patient from the repair group, as there was a serious mitral valve regurgitation during follow-up. At the end of the fourth year, we detected a mild degree of tricuspid valve impairment in two patients. The mean pulmonary artery pressure decreased significantly, and the patients' NYHA class improved to Class I-II. There was no recurrence of endocarditis in any of the patients at the end of the follow-up.

DISCUSSION

More than 50 to 70% of patients with IE are referred to a hospital with cardiovascular or systemic symptoms such as fever, heart failure, sepsis, anorexia within two to four weeks after the initiation of IE.[5-7] In the present study, we used modified Duke criteria for the definitive diagnosis of IE.[12] In patients with IE symptoms, positive blood culture from two separate blood samples, TTE with an oscillating intracardiac mass on valves, new onset of valvular regurgitation, or periannular abscess, as well as the partial dehiscence of prosthetic valve were the main diagnostic criteria. Rheumatic cardiac disorder, congenital heart defects, and previous valve surgery are the main risk factors of IE.[8-10] In the initiation of the treatment of IE, it is essential that the microorganism should be eradicated using broad-spectrum antibiotics to reduce mortality, morbidity, and the recurrence of IE. Cardiac surgery in confirmed patients is the primary treatment method following antimicrobial therapy in elective patients.[7-10]

In the current study, we presented our surgical experiences of 28 patients who had an IE in the urgent or elective setting. We also demonstrated the causative microorganisms in our series with IE, pre- and postoperative echocardiographic results, surgical approaches, and mortality rates. Microorganisms and TTE results were similar to previous reports.[11,12] In our cohort, dyspnea with low oxygen saturation related to a pulmonary embolic event in patients with an isolated right-sided or left-sided accompanied with left-sided IE, who required early surgery, was observed. Based on these findings, we suggest thoracic computed tomography (CT) in these particular cases, even if their hemodynamic status is stable with dyspnea to confirm pulmonary embolic events prior to surgery. According to our clinical experience, in the NYHA Class III and IV patients who underwent emergency surgery, the use of inotropic agents was higher, while the duration of intubation and length of hospital stay were longer. However, further randomized clinical studies are needed to draw more reliable conclusions on this subject. In our study, no statistically significant difference was observed when ECC and aortic cross-clamp times were compared with repair and single-valve replacement procedures. However, ECC and aortic cross-clamp times were significantly longer in double-valve replacement.

Baddour et al.[6] reported that IE was a complex disease requiring management by a team of physicians and health providers. Previous reports and guidelines[5-7,10] and previous meta-analyses describe the management of patients with IE. According to the clinical variations and complex situations of IE, the experienced surgeons may dictate some recommendations to the clinicians in the management

of AI for individual patients. Management of IE may be performed according to the clinical status of patients with IE by an experienced team including a cardiologist, an infectious disease specialist, and a cardiac surgeon.

Before the development of early diagnostic techniques and a broad range of antibiotics, uncontrolled septic shock and embolic events were mainly responsible for the mortality and morbidity in patients with IE.[2,8] Thanks to specific and a broad range of antimicrobial agents administrated immediately after the diagnosis and also owing to a multidisciplinary approach, the survival rates of patients have increased up to 80 to 90%.[7-10]

Multidisciplinary approach is important topic to decrease the mortality and morbidity of patients with AI. Despite advances in early diagnosis and treatment, AI still has a high mortality, and for a favorable outcome, it is very important to determine the optimal surgical timing.[7-9] The use of mechanical or bioprosthetic heart valves,[13] and the various kinds of surgical approaches, such as replacement or repair,[14,15] were compared in large-case series. No significant difference was found between patients who underwent mechanical or bioprosthetic valve implantation. Therefore, age of the patient, the presence of comorbid disorders, and surgeons' preferences may be considered while deciding the type of valve selection. The surgeons preferred valve replacement following an extensive excision of perivalvular and valvular tissues in these patients, particularly in complicated patients.

In a retrospective study, Berdajs et al.[15] investigated postoperative atrioventricular block following mitral valve replacement and mitral valve annuloplasty. They suggested valve repair in eligible patients, since the atrioventricular block and reoperation rates were significantly lower in patients who underwent valve repair in various case series in experienced centers. Gottardi et al.[16] also showed that IE was not seen again and there was no valve leakage in the follow-up of patients with isolated tricuspid valve endocarditis who underwent valve repair surgery. They suggested tricuspid valve replacement in patients with severe valvular destruction. We, therefore, performed tricuspid or mitral valve repair in six patients in our study. Preoperative TTE showed no evidence of complications related to an infection such as congestive heart failure, embolic event, or perivalvular abscess formation in these patients. We only observed severe valvular regurgitation in one patient who needed mitral valve replacement during follow-up. Since the majority of patients in our cohort were older than 60 years, we preferred bioprosthetic valve replacement. Rostagno et al.[17] suggested mitral valve repair, which was associated with a favorable clinical long-term outcome, when technically possible. Podesser et al.[18] also proposed mitral valve reconstruction in IE with a low incidence of valve-related complications with postoperative good results and survival.

Antibiotherapy alone or surgery following antibiotics has been previously compared in the treatment of IE. Alvarado-Alvarado et al.[19] reported that the patients who underwent surgery had lower mortality than the patients who only received medical treatment. They found the mortality rate in the medical and surgical treatment group to be 34.3% and 65.7%, respectively (p=0.049). According to the experiences of clinics, surgical treatment is accepted as the gold standard strategy for IE. In the study of Oylumlu et al.,[11] 110 patients with IE required surgery with a 28% mortality rate, as they had severe valvular destruction. Kocabas et al.[20] also reported their 15-year experiences in 210 patients with active IE and similar to previous studies,[13,14] the main causes of IE were previous prosthetic valve replacement and rheumatic valvular disorders. The mortality factors in the study were embolic events and congestive heart failure. In a small number of patients with IE, Tiryakioğlu et al.[13] proposed early surgery, if there was a valvular involvement by IE. They suggested that the indication of surgical treatment should be planned accordingly with the patients' condition and TTE results.

Indications for urgent or elective surgery and mortality factors in patients with an isolated left-sided or right-sided IE are well described.[10-13,18,20] Remadi et al.[21] showed that the clinical results of IE due to *S. aureus* were poor, particularly in patients with comorbid disorders, or with the presence of congestive heart failure, sepsis, as well as major neurological events. Early surgery is independently associated with reduced overall mortality and should be considered in selected cases to improve the outcome.[8,13,21-23] Inadequate control of sepsis or heart failure, intracardiac abscess, serious and paravalvular regurgitation, and prevention of embolic events in

patients with a large and mobile vegetations require early surgery.[8-10,17-19,21,22] Some authors have proposed tricuspid valve repair instead of valve replacement in patients with an isolated right-sided IE.[21,23] No significant difference was found when compared with the clinical outcomes after implantation bioprosthetic and mechanical valve in previous study.[24] However, Toyoda et al.[24] suggested that the surgeons could be used cardiac valve according to patients' characteristics in a large series. Dereli et al.[25] reported a 74-year-old female patient with prosthetic valve endocarditis who previously underwent mitral valve replacement. They performed redo-mitral valve replacement using a bioprosthetic valve in surgery.

Previous reports of IE include non-homogenous groups and different mortality rates.[21,23] Some authors have demonstrated that if surgery is performed with optimal timing, it may be possible to reduce the risk of mortality in the treatment of IE.[9-11,13] Thus, it should be kept in mind that the common consensus issued by the international and national scientific committees in the diagnosis, treatment, and reduction of mortality in patients with IE significantly contributes to the prevention of patient mortality and morbidity.

According to our experiences, pulmonary embolic events were more common in a limited but important case series in patients who had a right-side involvement of IE. We, therefore, suggest a thoracic CT for the confirmation of a pulmonary embolic event in patients with respiratory symptoms. To prevent morbidity and mortality, similar to previous authors, we propose early surgery in the presence of perivalvular abscess formation, congestive heart failure, or embolic events to reduce the mortality and morbidity rates.

In our study, we observed positive blood culture in 67.8% of patients. Staphylococci were the most commonly seen microorganisms in our cohort. Cardiac or pulmonary complications were common complications in our case series. Pulmonary infarction and localized abscess along with pleural effusions were detected in our two patients with an isolated right heart involvement in IVDU. As a result, pulmonary embolism should be ruled out with thoracic CT in case of respiratory distress. Although we had a limited number of cases, according to our clinical experience, we recommend early surgical intervention in patients whose liver enzymes and kidney function tests are impaired during medical treatment, even if hemodynamic values are stable. However, we believe that further randomized clinical studies are needed to establish its effectiveness in the clinical setting.

In conclusion, the surgical principles of IE should be determined according to the patients' conditions and characteristics to provide satisfactory clinical results. Our main principle in surgical practice is to carefully re-inspect the infected heart valve during surgery, perform vegetectomy and the cleaning of infected tissues, then repair the valve in suitable patients. However, in the light of the current guidelines in the literature, wide resection is performed in complicated patients, as all infected tissue and the entire valve are removed, and then valve replacement is performed. In eligible patients, valve repair can be performed. Broad-spectrum antibiotics should be administered after surgery for four to six weeks until negative blood culture results are obtained at least two times postoperatively. If patients are older and have comorbidities, then a bioprosthetic valve may be preferred.

Declaration of conflicting interests

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Clues on electrocardiography to predict the presence of paroxysmal atrial fibrillation in patients with acute ischemic stroke: A propensity score-matched study

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ABSTRACT

Objectives: In this study, we aimed to detect surface electrocardiography (ECG) markers that could be predictive of paroxysmal atrial fibrillation (PAF) attacks in patients with ischemic stroke.

Patients and methods: Between November 2017 and April 2021, a total of 112 patients (65 males, 47 females; mean age: 70.5±6.8 years; range, 51 to 84 years) hospitalized for acute ischemic stroke with sinus rhythm on surface ECG who underwent Holter ECG monitoring for PAF were retrospectively analyzed. The patients were divided into two groups of 56 patients in each (Group 1: those with PAF on Holter ECG and Group 2: those without PAF). Both groups were matched according to demographic, clinical, and echocardiographic features using the propensity score matching method.

Results: Demographic, clinical, and echocardiographic features were similar between groups (p>0.05). The mean maximum P-wave duration (PWD) and P-wave dispersion (PWDis) were longer in Group 1 than Group 2 (108.4±9.9 *vs.* 102.5±10.2 ms; p=0.002, 49.4±13.6 *vs.* 36.8±11.7 ms; p<0.001). Similarly, the mean P-wave terminal force in lead V_1 ($PTFV_1$) was higher in Group 1 than Group 2 (4415±909 *vs.* 3826±568 μV·ms; p<0.001). Logistic regression analysis revealed high PWDis (odds ratio [OR]: 1.164; 95% confidence interval [CI]: 1.069-1.268; p<0.001) and $PTFV_1$ (OR: 1.156; 95% CI: 1.065-1.254; p=0.001) as independent predictors of PAF.

Conclusion: PWDis and $PTFV_1$ are independent predictors of PAF in patients with acute ischemic stroke. These simple and easily accessible predictors that can be detected via surface ECG may be used as a guide to identify patients who require longer rhythm monitoring to better detect occult PAF, thereby preventing recurrent strokes.

Keywords: Atrial fibrillation, ischemic stroke, P-wave dispersion, P-wave terminal force in lead V1.

Atrial fibrillation (AF) is one of the most frequent cardiac rhythm abnormalities. Although its prevalence in the general population is thought to be around 2 to 4%, it is expected that it would increase by 2.3 times as life expectancy increases and advanced investigation techniques lead to overdiagnosis.[1] Diabetes mellitus, advanced age, hypertension, chronic renal failure, coronary artery disease, heart failure, obesity and obstructive sleep apnea are all important predisposing factors for AF.[1,2] Also, AF can lead to serious complications such as heart failure, stroke and death.[3] While the risk of AF associated stroke is 1.5% in the sixth decade of life, this risk increases to 24% in the ninth decade.[4] Similar to clinically overt AF, paroxysmal atrial fibrillation (PAF) attacks also increase the risk of ischemic stroke. Current guidelines recommend monitoring with Holter electrocardiography (ECG) to detect PAF attacks in patients with ischemic stroke, even if the surface ECG is normal.[5] Currently, 24 to 48-h Holter ECG monitoring is used for this purpose. However, existing silent PAF attacks cannot be detected with these recordings in some cases. Identifying patients at high risk for the development of AF before resorting to Holter ECG monitoring may help to improve diagnostic accuracy. In such high-risk patients, monitoring may be extended, if AF is not detected on 24 to 48-h Holter ECG recordings, thereby preventing false-negative results.

Many previous studies have investigated the use of several different scoring systems to identify patients

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who are under high risk for development of AF.[6,7] However, many of these systems are complex and difficult to use in daily practice. In the present study, we aimed to determine surface ECG findings that could predict the presence of PAF in those with ischemic stroke.

PATIENTS AND METHODS

This single-centre, retrospective study was conducted at Izmir Bakırçay University, Department of Cardiology between November 2017 and April 2021. A total of 149 patients with an ischemic cerebrovascular event (CVE) that had sinus rhythm on baseline surface ECG and underwent 24 to 48-h Holter ECG for cardioembolic investigation were screened. The patients were matched with the propensity score matching method in terms of their baseline clinical, demographic, and echocardiographic characteristics, which may be risk factors for AF, at a ratio of 1:1, and 56 each with and without PAF on Holter ECG a total of 112 patients (65 males, 47 females; mean age: 70.5±6.8 years; range, 51 to 84 years) were included in the study. Those with PAF detected on Holter ECG were defined as Group 1 (n=56) and those without it were defined as Group 2 (n=56). Patients under 18 years of age, those with serious renal or hepatic insufficiency, rheumatic moderate to severe mitral valve stenosis, prosthetic heart valve, previous history of AF, those who did not have normal sinus rhythm on basal ECG and those with missing or insufficient data on ECG or Holter ECG records were excluded from the study. The study protocol was approved by the Bakırçay University Non-Interventional Clinical Research Ethics Committee (No: 2021-333). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients' clinical, demographic, laboratory and ECG were obtained from the patient records. Baseline 12-lead surface ECG records were analyzed in detail. The 24 to 48-h Holter ECG recordings were evaluated by two cardiology specialists with the presence and length of PAF attacks noted.

Electrocardiography

During hospitalization with patients in the supine position, a 12-lead ECG was recorded from all subjects using 10 mV/cm standardization with 25 mm/sec paper speed and 0.05 to 100 Hz filter band settings. The ECGs were scanned and transferred to the computer system and measurements were made with an electronic caliper at 4× magnification on the high-resolution computer screen. P-wave dispersion (PWDis) was calculated as the difference between the maximum and minimum P wave duration (PWD) in all 12 ECG leads. P-wave terminal force in lead V_1 ($PTFV_1$) was defined as the duration multiplied by the amplitude of the negative part of the P wave (P'duration (a) × P'amplitude (b)), measured in μV ms in lead V1 (Figure 1).

Detection of an AF attack of at least 30 sec on Holter ECG was defined as PAF.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 25.0 software (IBM Corp., Armonk, NY, USA). A propensity score for the presence of PAF was estimated for each patient with logistic regression, using 26 clinically relevant baseline variables. Thereafter, using 1:1 matching without replacement, a matched cohort was constructed matching each patient without PAF to the closest patient with PAF in which propensity score differed by 0.1 or less. The ability to balance baseline features was evaluated by absolute standardized differences (the percentage difference between the means for the two groups divided by the reciprocal standard deviation). In standard differences, 10% were considered inconsequential. After matching, the overall balance p value was calculated as 0.99.

The normality distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Continuous variables were expressed in mean ± standard deviation (SD) and categorical variables were expressed in number and frequency. The groups were compared using the independent Student t-test or Mann-Whitney U test according to the normality distribution for continuous variables, and the chi-square test or Fisher exact test for categorical

Figure 1. P-wave terminal force measurement in lead V1 ($PTFV_1$) = **(a)** P'duration × **(b)** P'amplitude.
$PTFV_1$: P wave terminal force in lead V_1.

variables. The ECG findings were evaluated with logistic regression analysis to identify independent predictors of the presence of PAF on Holter ECG. Optimal cut-off values were determined by receiving operating characteristics (ROC) curve analysis to predict PAF. A *p* value of <0.05 was considered statistically significant.

RESULTS

Previous to ischemic stroke, 61.6% of patients (n=69) had a diagnosis of hypertension, 41.1% (n=46) had hyperlipidemia, and 33.9% (n=38) had diabetes mellitus. A previous history of CVE was present in 17.9% (n=20) patients. Coronary artery disease was present in 24.1% (n=27) and chronic heart failure in

Table 1
Baseline clinical characteristics and medications of matched patients

	Group 1 (n=56)			Group 2 (n=56)				
Variables	n	%	Mean±SD	n	%	Mean±SD	Standard differences	*p*
Clinical features								
Age (year)			70.6±7.1			70.2±6.5	0.052	0.782
Sex								
Male	33	58.9		32	57.1		0.017	0.848
Hypertension	33	58.9		36	64.3		0.053	0.560
Diabetes mellitus	19	33.9		19	33.9		0	1
Hypercholesterolemia	24	42.9		22	39.3		0.035	0.701
Chronic renal failure	8	14.3		9	16.1		0.017	0.792
CVD history	9	16.1		11	19.6		0.035	0.622
Coronary artery disease	14	25		13	23.2		0.017	0.825
Chronic heart failure	4	7.1		3	5.4		0.017	0.696
Thyroid disease	2	3.6		2	3.6		0	1
COPD	1	1.8		1	1.8		0	1
Carotid artery disease	26	46.4		28	50		0.071	0.611
CHA2DS2-VASc score			4.9±1.2			4.8±1.3	0.013	0.826
LVEF (%)			57.7±5.7			58.1±4.2	0.048	0.779
Left atrium diameter (mm)			37.1±3.5			37.1±4.4	0.004	0.981
LVDD	28	50		27	48.2		0.017	0.850
Severe mitral regurgitation	1	1.8		1	1.8		0	1
Medications								
Acetylsalicylic acid	13	23.2		15	26.8		0.035	0.663
Clopidogrel	10	17.9		9	16.1		0.017	0.801
Oral anticoagulant	2	3.6		1	1.8		0.017	0.390
Statin	11	19.6		9	16.1		0.035	0.622
Beta-blocker	13	23.2		14	25		0.017	0.825
Calcium channel blocker	19	33.9		18	32.1		0.017	0.841
ACEi or ARB	18	32.1		21	37.5		0.053	0.552
Levothyroxine	1	1.8		1	1.8		0	1
Methimazole	1	1.8		0	0		0.017	0.315

SD: Standard deviation; CVD: Cerebrovascular disease; COPD: Chronic obstructive pulmonary disease; LVEF: Left ventricular ejection fraction; LVDD: Left ventricular diastolic dysfunction; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

Table 2
Laboratory characteristics of patients according to groups

Variables	Group 1 (n=56) Mean±SD	Group 2 (n=56) Mean±SD	*p*
Fasting blood glucose (mg/dL)	125.1±37.4	135.5±49.2	0.214
Urea (mg/dL)	39.8±17.5	42.9±23.2	0.370
Creatinine (mg/dL)	1.1±0.8	0.9±0.3	0.207
Sodium (mEq/L)	138.9±2.9	138.6±3.0	0.653
Potassium (mg/dL)	4.4±0.6	4.3±0.4	0.166
Total cholesterol (mg/dL)	183.0±40.1	195.5±41.0	0.822
LDL-cholesterol (mg/dL)	111.9±34.7	116.5±35.4	0.723
Plasma triglycerides (mg/dL)	143.5±59.5	193.2±101.1	0.009
HDL-cholesterol (mg/dL)	41.7±11.2	39.1±9.4	0.198
TSH (mU/L)	2.2±4.8	1.9±1.6	0.715
Free T4 (ng/dL)	1.3±0.4	1.2±0.2	0.961
White blood cell count ($\times10^9$/L)	9.0±2.4	8.4±2.9	0.497
Neutrophil count ($\times10^9$/L)	6.0±2.1	5.5±2.6	0.558
Lymphocyte count ($\times10^9$/L)	2.0±0.8	2.0±0.9	0.938
Hemoglobin (g/dL)	12.9±1.6	13.0±1.9	0.224
Hematocrit (%)	38.4±4.5	38.6±5.3	0.199
Platelet count ($\times10^9$/L)	266.1±90.7	253.6±84.8	0.369

SD: Standard deviation; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TSH: Thyroid-stimulating hormone.

6.3% (n=7) patients. Fifty-four (48.2%) patients had carotid artery disease and, of these patients, 34 had carotid artery stenosis <50% and 20 had stenosis ≥50%. The mean CHA2DS2-VASc score of patients was 4.9±1.3. The mean left ventricular ejection fraction was 57.9±5.1% and the mean left atrial (LA) diameter was 37.1±4.1 mm. When CVE occurred, 25% (n=28) patients were using acetylsalicylic acid, 17% (n=19) clopidogrel and 2.7% (n=3) were taking oral anticoagulant therapy. Patients' demographic and clinical features are shown in Table 1 and their laboratory findings are shown in Table 2.

Both groups were similar with regard to the mean baseline heart rate (74.4±13.2 *vs.* 74.6±10.8 bpm, p=0.93). The mean maximum PWD and PWDis were longer in Group 1, compared to Group 2 (108.4±9.9 *vs.* 102.5±10.2 ms; p=0.002 and 49.4±13.6 *vs.* 36.8±11.7 ms; p<0.001, respectively). Similarly,

Table 3
Baseline electrocardiographic characteristics of patients according to groups

Variables	Group 1 (n=56) Mean±SD	Group 2 (n=56) Mean±SD	*p*
Heart rate (bpm)	74.4±13.2	74.6±10.8	0.931
Maximum P wave duration (ms)	108.4±9.9	102.5±10.2	0.002
P wave dispersion (ms)	49.4±13.6	36.8±11.7	<0.001
$PTFV_1$ (μV·ms)	4415±909	3826±568	<0.001

SD: Standard deviation; bpm: Beats per minute; ms: Millisecond; $PTFV_1$: P wave terminal force in lead V_1.

Table 4
Effects of ECG indicators on the detection of paroxysmal atrial fibrillation in univariate and multivariate logistic regression analysis

	Univariate logistic regression			Multivariate logistic regression		
Variables	OR	95% CI	*p*	OR	95% CI	*p*
Maximum P-wave duration	1.061	1.019-1.104	0.004	0.913	0.825-1.010	0.078
P-wave dispersion	1.082	1.044-1.121	<0.001	1.164	1.069-1.268	<0.001
$PTFV_1$	1.109	1.042-1.180	0.001	1.156	1.065-1.254	0.001

OR: Odds ratio; CI: Confidence interval; $PTFV_1$: P wave terminal force in lead V_1.

$PTFV_1$ was higher in Group 1, compared to Group 2 (4415±909 *vs.* 3826±568 μV·ms; p<0.001) (Table 3).

Logistic regression analysis demonstrated high PWDis (odds ratio [OR]: 1.164; 95% confidence interval [CI]: 1.069-1.268; p<0.001) and high $PTFV_1$ (OR: 1.156; 95% CI: 1.065-1.254; p=0.001) as being independent predictors for the presence of PAF (Table 4). As predictors for the presence of PAF, the ROC curve analysis revealed a sensitivity of 71% and specificity of 69% for PWDis >42 ms (area under the curve [AUC] 0.764, 95% CI: 0.675-0.852, p<0.001) and a sensitivity of 60% and specificity of 64% for $PTFV_1$ >4.050 μV·ms (AUC: 0.686, 95% CI: 0.574-0.798, p=0.002) (Figure 2).

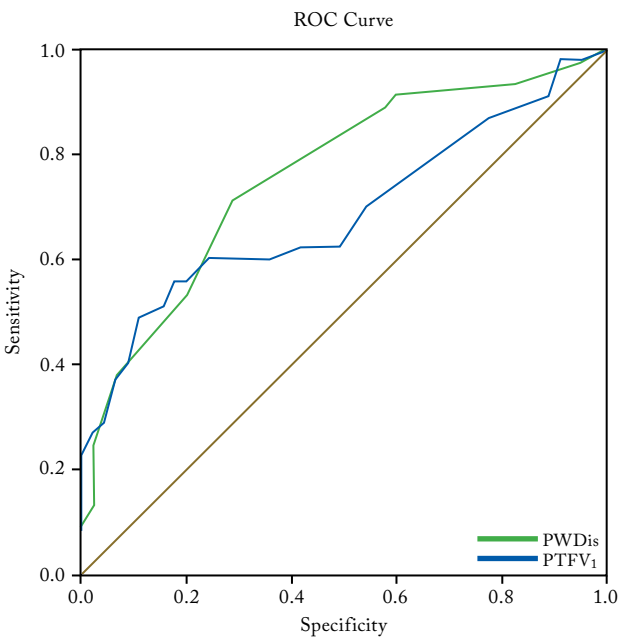

Figure 2. Receiver operating characteristic (ROC) curve analysis of the optimal cut-off values of P-wave dispersion and P-wave terminal force in lead V_1.

PWDis: P-wave dispersion (PWDis; $PTFV_1$: P wave terminal force in lead V_1.

DISCUSSION

In the present study, we found that PWDis and $PTFV_1$ parameters as measured on surface ECG were independent predictors for the presence of PAF in patients with ischemic stroke.

Some patients with AF describe palpitations, shortness of breath and fatigue while some may be completely asymptomatic and present with complications such as ischemic stroke or tachycardiomyopathy.[8] Non-valvular AF is responsible for about half of all cardioembolic events.[9] The incidence of occult or subclinical AF is not known. Therefore, patients with symptomatic AF that are observed in daily practice may be considered the tip of the iceberg. The development of new devices and applications has led to an increase in diagnosis rates of asymptomatic and subclinical AF. The rates of subclinical AF was reported to be 35% in a group of patients with implanted cardiac devices that were followed for 2.5 years.[10] In patients with cryptogenic stroke, 12.5% were found to have PAF attacks during one-year rhythm monitorization.[11] It is important to identify patients who do not have arrhythmia on surface ECG, but who are at high risk for the development of AF and to perform long-term rhythm monitoring in these patients to prevent ischemic stroke.

Many scoring methods have been utilized to predict the development of AF in those with normal surface ECG.[6,7] The CHADS2 and the CHA2DS2-VASc risk scores have been reported for prediction of new occurrence of AF, ischemic stroke and long-term outcomes after AF ablation.[12] Christophersen et

al.[12] reported that CHARGE-AF scoring was better at predicting AF, compared to CHA2DS2-VASc. On the other hand, some studies have used the HATCH score for prediction of AF recurrence and persistence.[13] The main feature of these scoring methods is that they predict the development of AF according to the clinical characteristics of the patients. However, AF is an ECG disorder and using ECG findings for its prediction may be a more plausible way. Electrocardiographic evaluation is also a simpler, cheaper, and easily accessible method than the aforementioned scoring systems. Furthermore, it has been reported that P-wave indices are as effective as clinical scoring methods for the prediction of AF and ischemic stroke.[14] Several ECG indices thought to represent atrial remodeling have been independently associated with stroke and AF.[15] These measures include the *(i)* PWD; *(ii)* PWDis; *(iii)* $PTFV_1$ in the precordial lead V1; *(iv)* P-wave axis; and *(v)* interatrial blocks (IABs).[16] Previous studies have identified several P-wave indices that are markers of LA dysfunction and are associated with ischemic stroke with or without AF.[17] Previous studies have reported that maximum PWD may be used for the prediction of AF.[18] However, we did not detect PWD to be a predictor for the presence of AF in our study.

P wave dispersion is considered to reflect impaired and heterogeneous interatrial conduction, which is a specific and sensitive marker of AF in a wide variety of conditions.[19] Dilaveris et al.[18] found that PWDis was significantly higher in patients with paroxysmal AF compared to the control group, and a PWDis value of 40 ms distinguished paroxysmal AF patients from the control group with a sensitivity of 83% and a specificity of 85%. Aytemir et al.[20] reported PWDis >36 ms to be an independent predictor for the development of AF with a sensitivity of 77% and specificity of 82%. The PWDis has been used for the prediction of AF in several clinical situations such as hyperthyroidism, chronic obstructive pulmonary disease, acute ischemic stroke and hypertrophic cardiomyopathy.[19] Doğan et al.[15] reported PWDis as an independent predictor for the development of AF in patients with acute ischemic stroke. Similarly, we also found PWDis to be a predictor of PAF in patients with ischemic stroke, with a sensitivity of 71% and specificity of 69%.

The $PTFV_1$ was first used by Morris et al.[21] in 1964 as a representative of LA overload in several valvular heart diseases. Later, $PTFV_1$ was found to be an indicator of various pathologies such as increased LA pressure, LA hypertrophy, LA enlargement, and abnormal interatrial conduction.[17] Since AF development is also associated with these structural changes and electrical remodeling, $PTFV_1$ may be a good predictor of AF development. $PTFV_1$ >4000 μV·ms is accepted to be abnormal. An abnormal $PTFV_1$ level has been shown to negatively affect prognosis in heart failure and myocardial infarction.[22] It was reported that a 1-SD increase of $PTFV_1$ increased the risk of AF occurrence by 27%.[17] Additionally, $PTFV_1$ was found to be a better predictor in hemodialysis and stroke patients compared to the normal population.[17] The $PTFV_1$ is indicative of LA volume overload and it has, therefore, been frequently used for AF prediction in patients undergoing hemodialysis.[17] Goda et al.[23] found $PTFV_1$ to be a strong predictor of AF in patients with acute ischemic stroke. In addition, $PTFV_1$ was reported to be a good predictor of stroke, regardless of AF in a meta-analysis by He et al.[24] However, Sajeev et al.[25] suggested that $PTFV_1$ was a weak predictor of ischemic stroke. Similarly, we found that $PTFV_1$ had a lower sensitivity and specificity in the detection of AF compared to PWDis.

There are some limitations in the current study. First, our sample size was relatively small, which may have weakened the strength of our results. Second, this study is retrospective in nature. Third, Holter ECG monitoring was performed for 24 to 48 h in all patients. If a longer follow-up could have been made, PAF attacks could have been detected in more patients.

In conclusion, PWDis and $PTFV_1$ in lead V1 are independent predictors for the presence of PAF in patients with ischemic stroke. These simple and easily accessible predictors, which can be detected by surface ECG, may help in identifying patients that require longer rhythm monitoring to detect occult PAFs, thereby preventing recurrent strokes.

Declaration of conflicting interests

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In which cases of beta-blocker intoxication in childhood, does hypoglycemia develop more easily?

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ABSTRACT

Objectives: In this study, we aimed to investigate factors which could facilitate the identification of hypoglycemia in beta-blocker (BB) intoxication cases.

Patients and methods: Between November 2020 and November 2021, a total of 136 patients (53 males, 83 females; mean age: 11.6+5.7 years; range, 2 to 17 years) who were admitted to the emergency department with BB poisoning were included in the study. The data on the cases were taken from the hospital's automation system.

Results: The mean systolic blood pressure (SBP) was 86.2±12 mmHg, the mean heart rate (HR) was 72.9±12.2 bpm, and the mean blood glucose level (BGL) was 104.4±42.8 mg/dL. When the relationship between the HR, SBP, and BGL of the cases was examined, there was a poor positive correlation between BGL and HR (r=0.32, p<0.01). No linear correlation was detected between BGL and SBP or between BGL and toxic dose percentage (r=0.23, p=0.06 and r=0.16, p=0.05). A very strong negative correlation was found between the percentage of toxic dose and SBP, and between the toxic dose percentage and HR (r=-0.90, p<0.01 and r=-0.76, p=0.04). There was a weak positive correlation between HR and SBP (r=0.42, p=0.09).

Conclusion: We found a correlation between the decrease in HR and the decrease in BGL. Younger age, female sex, and high dose of the drug facilitated the development of hypoglycemia.

Keywords: Beta-blocker poisoning, hypoglycemia, pediatric emergency.

Poisoning is one of the most preventable causes of child fatalities, and in the United States (US), approximately 1.5 million children are admitted to emergency departments each year due to poisoning.[1] Drugs and corrosive substances are the two largest causes of poisoning worldwide, drugs that affect the central nervous system and cardiovascular system (CVS) constitute the largest number of poisoning cases, and poisoning with beta-blockers (BBs) is particularly common.[1-3] According to the 2004 Toxic Exposure Surveillance System Report, in the US, there were 4,077 BB intoxication case admissions among children under the age of six years old.[4]

In BB poisoning cases, cardiovascular effects (bradycardia, hypotension, myocardial depression, and cardiogenic shock), mental status change, seizure, hypoglycemia, and bronchospasm may occur.[5-7] Beta-blocker poisoning have become more common due to overuse of BBs. These medications are used to treat many diseases, including hypertension, ischemic heart disease, thyrotoxicosis, tremors, portal hypertension, migraine headaches, aortic dissection, arrhythmia, and heart failure. Therefore, this situation makes them easily accessible for children.[8] Cardiovascular effects determine the prognosis.[8-12] The development of hypoglycemia is another clinical condition that is commonly associated with BB intoxication. The development of hypoglycemia is frequently mentioned in the literature; however, this information is mostly based on old case reports and is not very common in daily practice. The mechanisms associated with the development of hypoglycemia depend on inhibiting

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glycogenolysis and gluconeogenesis, which reduces glucose production.[13] Therefore, blood glucose level (BGL) monitoring is vital in BB poisoning cases.

Hypoglycemia is typically defined as a BGL below 60 mg/dL in the presence of symptoms (e.g., sweating, tremor, tachycardia, hunger, lethargy, confusion, irritability, and seizure) or a BGL below 50 mg/dL in the absence of symptoms.[14]

In the literature, there is no study indicating which BB poisoning cases develop into hypoglycemia more frequently. The primary objective of this study was to investigate which characteristics in patients with BB intoxication might be predictive factors for the development of hypoglycemia. The secondary objective was to determine how cardiovascular findings (e.g., heart rate [HR] and systolic blood pressure [SBP]), the main determinants of mortality, were affected in BB poisoning cases.

PATIENTS AND METHODS

This single-center, retrospective, cross-sectional, observational study was conducted at Pediatric Emergency Clinic of Izmir Tepecik Training and Research Hospital Pediatric Poisoning Center between November 2020 and November 2021. Patients aged between 0 and 18 years who were admitted to the emergency department with BB poisoning were included in the study. Patients with a disease affecting the CVS or altering glucose metabolism and those who used drugs that affect these systems were excluded from the study. Finally, a total of 136 patients (53 males, 83 females; mean age: 11.6+5.7 years; range, 2 to 17 years) were included. A written informed consent was obtained from all parents and/or legal guardians of the patients. The study protocol was approved by the Izmir Katip Çelebi University Non-Interventional Clinical Studies Instutional Review Board Ethics Committee (date/no: 2020-GOKAE-0062). The study was conducted in accordance with the principles of the Declaration of Helsinki. The data were obtained from the hospital's automation system. After examining the characteristics of each case, such as age, sex, and the type of drug that they ingested, the HR, SBP, and BGL measurements of the cases were noted. While the independent variable of this study was BGL, its dependent variables were age, sex, HR, and SBP. Cases were categorized as normocardic and bradycardic, considering normal values of HR according to age.[15,16] Cases were also categorized as normotensive or hypotensive, considering the normal values of SBP according to age.[15,16] Cases were evaluated as hypoglycemic when BGLs were below 60 mg/dL and normoglycemic when BGLs were 60 mg/dL or higher.[17] The amount of BB received by the cases was rated according to the specific toxic dose of each drug. The percentage of exposure was calculated one by one according to how much of the toxic dose was exposed. This value is termed as the "percentage of toxic dose" (PTD), and the table below lists the accepted toxic doses of the drugs (Table 1).

Statistical analysis

When the acceptable margin of error was set at 1.5%, a minimal sample size at 80% power was determined to be 108 cases. 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

Table 1
Toxic doses and half-lives of some beta-blocker agents for childhood[27]

Beta-blockers	Toxic dose	Half-life (hours)
Metoprolol (mg/kg)	2.5	4-20
Propranolol (mg/kg)	4	3-4
Atenolol (mg/kg)	2	6-9
Bisoprolol (mg/kg)	10	9-12
Betaksolol (mg) (for adults)	20	14-24
Acebutolol (mg/kg)	12	3-4
Sotalol (mg/kg)	4-10	12

Table 2
Age and sex characteristics of groups and beta-blocker drugs to which they were exposed

	n	%	Mean±SD	Min-Max
Age (year)			11.6±5.7	2-17
Sex				
Female	83	61		
Male	53	39		
Drugs exposed to				
Metoprolol	39	28.7		
Propranolol	49	36		
Atenolol	11	8.1		
Bisoprolol	12	8.8		
Betaxolol	13	9.6		
Acebutolol	8	5.9		
Sotalol	4	2.9		

SD: Standard deviation.

frequency. The chi-square test was used to compare categorical data, and the Fisher exact test was used when the chi-square assumptions could not be provided. The t-test was applied to compare numerical variables. The Pearson correlation analysis was carried out to investigate the relationships between numerical variables. Logistic regression modelling was performed to predict the risk factors for the development of hypoglycemia; the forward stepwise technique was used. A p value of <0.05 was considered statistically significant.

RESULTS

The BB drug patients were exposed to were propranolol (36%), metoprolol (28.7%), betaxolol (9.6%), bisoprolol (8.1%), acebutolol (5.9%), and sotalol (2.9%). The mean SBP was 86.2±12 (range, 57 to 140) mmHg, the mean HR was 72.9±12.2 (range, 56 to 110) bpm, and the mean BGL was 104.4±42.8 (range, 42 to 200) mg/dL (Table 2).

Based on the mean values of the SBP, HR, and BGL of female and male cases at the time of admission, the mean SBP of females was 85.3±8.6 mmHg, the mean HR was 75.5±13.1 bpm, and the mean BGL was 89.7±20.4 mg/dL. Among males, the mean SBP was 87.7±15 mmHg, the mean HR was 68.5±8.9 bpm, and the mean BGL was 127.5±56.7 mg/dL (p=0.03, p=0.04, p<0.01, respectively) (Table 3). The calculated PTD in male cases was significantly higher than in female cases (p=0.01).

Considering the normal values of the patients according to their age, their blood pressure values were hypotensive or not one by one. Accordingly, 57 (41.9%) cases were hypotensive and 79 (58.1%) cases were normotensive. Seven (12.3%) cases in the

Table 3
Distribution of heart rate, systolic blood pressure, and blood sugar levels by age and sex

	Female (n=83)	Male (n=53)			
	Mean±SD	Mean±SD		p	t
Systolic blood pressure (mmHg)	85.3±8.6	87.7±15		0.03	1.6
Heart rate (/min)	75.5±13.1	68.5±8.9		0.01	4.2
Blood glucose level (mg/dL)	89.7±20.4	127.5±56.7		<0.01	5.5
Percentage of toxic dose (%)	161.9±47	171.1±67.3		0.01	-0.9
	≤6 years (n=48)	>6 years (n=88)			
	Mean±SD	Mean±SD	Min-Max	p	t
Systolic blood pressure (mmHg)	84.6±8.6	87.1±13.4		0.04	1.1
Heart rate (/min)	78.6±14	69.8±9.1		<0.01	4.8
Blood glucose level (mg/dL)	79.3±18.4	118.2±46		<0.01	5.6
Percentage of toxic dose (%)	155.1±2.1	171.1±32		0.7	-1.6
Blood glucose level (mg/dL) (whole group)	104.4±42.8		49-200		
Heart rate (/min) (whole group)	72.9±12.2		56-110		
Sistolik blood pressure- (mmHg) (whole group)	86.2±12		57-140		

SD: Standard deviation.

Table 4
Distribution of bradycardia and hypotension status of cases in groups by age and sex

	Hypotensive cases (n=57), (100%)		Normotensive cases (n=79), (100%)			Bradycardic cases (n=41), (100%)		Normocardic cases (n=95), (100%)		
	n	%	n	%	*p*	n	%	n	%	*p*
≤6 years (n=48)	7	12.3	41	51.9	<0.01	24	58.5	24	25.2	<0.01
>6 years (n=88)	50	87.7	38	48.1		17	41.5	71	74.7	
Female (n=83)	26	45.6	57	72.2	0.03	25	61	58	61.1	0.5
Male (n=53)	31	54.4	22	27.8		16	39	37	38.9	

hypotensive group were under the age of six, and 26 (45.6%) cases in the hypotensive group were female. Forty-one (51.9%) cases in the normotensive group were under the age of six, and 57 (72.2%) cases in the normotensive group were girls. Although the mean SBP was higher in the cases over six years old, the number and rate of individuals exceeding the hypotension limit were found to be significantly higher in the cases over six years old (Table 4). The mean of the PTD was determined to be higher in the cases older than six years than in the younger cases (p=0.7).

The cases were evaluated according to the normal values for their ages, whether the patients were bradycardic or not. Accordingly, bradycardia was detected in 41 (30%) cases. Twenty-four (58.5%) of these 41 cases were under the age of 6 and 25 (61%) cases were girls. While the mean HR value was higher in patients younger than six years, the rate of bradycardia was significantly lower. No relationship was found between bradycardia and sex (Table 4).

When bradycardia status and hypotensive status were compared, normal SBP (78%) was found to be significantly higher in the bradycardic group. Hypotension was detected in 51.6% of those with normal HR. Eight cases were found to be both bradycardic and hypotensive (5.8% of the whole group). The rate of normal HR (86%) was significantly higher in the hypotensive group (p=0.01) (Table 5).

When the relationship between the HRs, SBPs, and BGLs of the cases was examined, a positive poor correlation was found between BGL and HR (r=0.32, p<0.01). No linear correlation was found between BGL and SBP or between BGL and PTD (r=0.23, p=0.06 and r=0.16, p=0.05). A very strong negative correlation was found between PTD-SBP and PTD-HR (r=-0.90, p<0.01 and r=-0.76, p=0.04). A positive poor correlation was found between HR and SBP (r=0.42, p=0.09) (Table 6).

Hypoglycemia was detected in 11 cases (8.1% of the whole group). Five of these cases received acebutolol, three received metoprolol, and three received propranolol. When these cases were examined, the rate of bradycardia in hypoglycemic cases was found to be significantly lower (9.8%) than the rate of bradycardia in normoglycemics (p=0.01). The hypotension rate in hypoglycemic cases was found to be significantly lower (7%) than in normoglycemics (p=0.03) (Table 7).

We used the parameters of age, sex, PTD, SBP, and HR levels that had significant values in the binary analyses for the logistic regression model to examine

Table 5
Relationship between bradycardia and hypotension status of the cases in the group

	Normocardic cases		Bradycardic cases		
	n	%	n	%	*p*
Normotensive cases	46	48.2	33	78	
Hypotensive cases	49	51.6	8	22	0.01
Total	95	100	41	100	

Table 6
Correlation analysis between heart rate, systolic blood pressure, and blood sugar levels

	R	*p*
BGL-HR	0.32	<0.01
BGL-SBP	0.23	0.06
BGL-PTD	0.16	0.05
PTD-SBP	-0.90	<0.01
PTD-HR	-0.76	0.04
HR-SBP	-0.42	0.09

BGL: Blood glucose level; HR: Heart rate; SBP: Systolic blood pressure; PTD: Percentage of toxic dose.

the factors that may cause hypoglycemia. According to the results of this model, being younger than six years increased the development of hypoglycemia by 2.99 folds, by 3.6 folds, and an increase in PTD increased the development of hypoglycemia by 1.04 folds (Table 8).

In our study, none of the cases died due to either cardiovascular causes or hypoglycemia.

DISCUSSION

The primary objective of our study was to determine the predictive factors for the development of hypoglycemia in cases with BB intoxication. We found a correlation between decreased HR and decreased BGL. In addition, younger age, female sex, and a higher dose of the drug taken facilitated the development of hypoglycemia. However, bradycardia and hypotension were not seen more frequently in cases with hypoglycemia.

The secondary objective of our study was to determine how HR and SBP were affected in cases with BB intoxication. In male cases, while the mean HR was lower, the mean SBP was higher than the female cases. Additionally, the mean HR was lower in those older than six years, while the mean SBP was higher. As the amount of medication taken increased, the mean HR and SBP decreased.

Among the consequences that occur in cases of BB intoxication, those related to the CVS are the most important. Morbidity is dependent on bradycardia

Table 7
Relationship between hypoglycemia-bradycardia and hypoglycemia-hypotension

	Normoglicemic cases		Hypoglicemic cases		
	n	%	n	%	*p*
Normocardic cases	88	70.4	7	63.6	
Bradycardic cases	37	29.6	4	36.4	0.01
Total	125	100	11	100	
Normotensive cases	72	57.6	7	63.6	
Hypotensive cases	53	42.4	4	36.4	0.03
Total	125	100	11	100	

Table 8
Logistic regression model created for the development of hypoglycemia

	B	S.E.	OR	95% Cl for Exp B	*p*
Age	1.09	0.36	2.99	1.4-6.06	0.02
Sex	12.7	4.3	3.6	7.06-18.5	0.03
Percentage of toxic dose	0.04	0.19	1.04	1.02-1.08	0.04
Systolic blood pressure	-0.5	0.92	0.55	0.09-3.4	0.5
Heart rate	0.8	1.1	2.33	0.2-20	0.4
Constant	-19.9	6.1	0.1	0.2-20	0.01

-2 loglikehood=44,496.

and/or hypotension. One of the studies on this subject was conducted by Love et al.[10] In this study, 280 BB poisoning cases were examined, and cardiotoxicity was found in 41 (15%) cases. Four (1.4%) of these 41 cases died, and these cases were additionally exposed to a different drug. In our study, no exitus cases were detected. The reason for this may be that those who used another drug were excluded from our study. Similarly, in a study conducted by Belson et al.,[18] BB-linked cardiotoxicity was found in 1.6% of the cases. This low rate of cardiotoxicity can be explained by how, in this study, 83% of the cases came from exposure to only a single tablet. In this study group, 272 of 280 patients were discharged without any problems, four were reported to have minor and four to have moderate effects. In childhood, BB agents are considered toxic, even for those taking a single tablet. It is undeniable that the toxicity potential increases if the number of drugs increases. In a study by Langemeijer et al.,[19] myocardial depression increased as the dose of BB increased. In our study, the term PTD was developed to calculate how much the drug taken exceeds the determined dose, how much the HR increases, and how much the SBP decreases at that rate.

In our previous study, our team compared the BGLs of patients who received BB with those of patients who took a selective serotonin receptor inhibitor (SSRI).[20] The purpose of using SSRIs was that these drugs usually do not cause hypoglycemia. It was shown that BB intoxication decreased BGLs compared to other poisoning instances, but these values were not serious hypoglycemic events. Based on this result, in the current study, we attempted to examine which characteristics of patients with BB poisoning might be risk factors for the development of hypoglycemia. We found a correlation between the decrease in HR and BGL. In addition, we found that younger age, female sex, and a high dose of the drug used facilitated the development of hypoglycemia. However, since there is no similar study in the literature, we could not find an opportunity to compare our results.

According to BB poisoning cases in terms of age and sex, in a study conducted by Love et al.,[4] 208 children with BB poisoning were examined and they found that 57% of the cases were under four years old and 57% of them were males.

In many studies about poisoning, boys are exposed to toxic agents at a younger age and girls in the adolescent ages.[21] According to a study conducted by Lauterbach et al.,[22] 59% of 2,967 cases with BB poisoning were found to be female in the adult age group. In our study, 64.7% of the cases were over six years old and 61% of them were females. We believe that the reason for identifying such a high number of female cases is that we included adolescents in our study group.

According to the relationship between age and cardiac function, at younger ages, toxins are more destructive to cardiac functions.[23] In our study, although the mean HR value was higher in patients younger than six years old, the rate of bradycardia was higher. This may be due to the increased sensitivity to bradycardia when the age gets younger. This is also why SBP is lower in those younger than six years old. However, the fact that the number of cases exceeding the hypotension limit is higher in those over six years of age can be explained by the higher amount of drugs taken in the older age group (where the percentage of the toxic dose is higher than in the younger ones). Besides, BB agents show their cardiac effects through ß1-receptors first and they show vascular effects later.[24]

When we investigated which BBs were seen most frequently in cases of BB poisoning, the most common three BBs were atenolol, metoprolol, and propranolol in Love et al.'s studies.[4,6] Similarly, in our study, the most common poisoning agents were propranolol and metoprolol. Even in Love et al.'s[10] study conducted in 2000, propranolol (43.2%) was found to be the most common BB, as in this study.

When we examine the pathological conditions that occur in cases poisoned with BB, Love et al.[4] found that bradycardia was detected only in a two-year-old patient who received 50 mg of atenolol out of 208 children who were followed in their study, and this case was resolved without any treatment. In the same study, in one case, BGL was determined to be 55 mg/dL, and in other cases, hypoglycemia was not observed. In a study by Litovitz et al.,[25] a seven-year-old girl presented with hypotension, hypoglycemia, aspiration, and asystole after propranolol intake.

In a study conducted by Eibs et al.,[26] out of 49 children who received BBs, 30 (61.2%) had bradycardia and/or hypotension as CVS effects. In addition to CVS effects, hypoglycemia was observed in 12 children. Most of the cases that developed hypoglycemia received propranolol.

Similarly, 90 (66.1%) patients had cardiovascular effects (hypotension and/or bradycardia) in our study. There are publications in the literature showing that children who develop hypoglycemia are mostly exposed to agents with high lipophilicity, such as propranolol, or high membrane-stabilizing activity (MSA), such as acebutolol.[9,10] In our study, cases who developed hypoglycemia were exposed to either high-MSA or high-liposolubility drugs, such as acebutolol, metoprolol, and propranolol.

In the literature, hypoglycemia associated with BB intoxication has been linked to prolonged fasting in non-diabetic cases.[21] In our previous study, our team compared the BGLs of 40 cases who received BBs and 40 cases who received SSRIs. There was no low BGL at the time of the first admission in the BB group, but BGL was significantly lower at 1 and 24 h of follow-up than in the SSRI group.[20] However, based on the cases that exceeded the hypoglycemia limit, there was no significant difference. These data suggest that, as in the literature, the low BGL might have been due to prolonged fasting, not drugs.

Based on the mortality of BB intoxication, Love et al.[6] examined 10-year poison control service reports and did not see any deaths under the age of six in 19,388 cases of BB intoxication. In Langemeijer et al.'s[20] study, they did not observe any exitus in the same age group. Similarly, there was no mortality in our study.

The limitation of our study is that the number of cases, particularly the number of cases developing hypoglycemia, is low. If there were more cases of hypoglycemia, it would be easier to evaluate risk factors. Our study was established with a retrospective design, as it aimed to investigate the risk factors of a result. However, in light of these data, in a prospective study in which patients with BB poisoning may have been monitored for a longer period, the late effects of BB may have been detected. Moreover, knowing the nutritional status of the cases and body mass indexes would contribute to eliminating the confounding factors that may cause hypoglycemia. However, our study would still contribute to the literature, since it is the first study of this subject focusing on childhood.

In conclusion, in our study, patients who were younger, who took a large amount of drugs, and whose HRs were lower were at a greater risk of developing hypoglycemia. Therefore, cases of BB poisoning with these characteristics should be monitored more closely for BGL.

Declaration of conflicting interests

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Cardiovascular Surgery and Interventions

Case Report Open Access

Retroperitoneal approach for suprarenal abdominal aortic aneurysm in Marfan syndrome

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ABSTRACT

Suprarenal abdominal aortic aneurysms pose a surgical challenge, as it is difficult to reanastomose the renal arteries and to place a cross-clamp to the aortic segment involving the visceral arteries through the diaphragmatic crux. The retroperitoneal approach with a limited thoracoabdominal incision through the ninth intercostal space offers some advantages over the midline transperitoneal approach which we explain by presenting its use in a patient with Marfan syndrome and a true abdominal aortic aneurysm. This technique should be in the armamentarium of aortic surgeons as they have to face with ever-increasingly difficult cases in the endovascular era.

Keywords: Aortic aneurysm/abdominal, juxtarenal aneurysm, Marfan syndrome, retroperitoneal approach, suprarenal aorta, surgery.

Suprarenal abdominal aortic aneurysms (AAAs) pose a surgical challenge due to its location. It is difficult to reanastomose the renal arteries to the aortic graft and to place a cross-clamp through the diaphragmatic crux to the aortic segment involving the visceral arteries. The exposure is the key to success in repair of the suprarenal AAAs. Midline transperitoneal (TP) and lateral retroperitoneal (RP) approaches are used for exposure. Retroperitoneal approach with a thoracoabdominal incision through the ninth intercostal space offers some advantages which we explain by presenting its use in a patient with Marfan syndrome.

CASE REPORT

A 46-year-old female patient with Marfan syndrome without any complaints was admitted for elective surgery due to enlarging suprarenal AAA which reached a diameter of 5.3 cm (Figure 1). The patient had a Bentall procedure with a mechanical valve 10 years ago in our institution and was under follow-up since then. Warfarin was discontinued three days before the operation. A written informed consent was obtained from the patient.

The patient was positioned with the left shoulder elevated nearly perpendicular to the table and the pelvis tilted slightly to the left. The operating table was fully broken head down to increase the space between the costal margin and the pelvis. An S-shaped incision was made that commenced at the left lateral edge of the rectus abdominis muscle at the umbilicus and extended to the costal margin then to the ninth rib space (Figure 2). Electrocautery was used to incise the abdominal wall musculature. The left chest was entered through the ninth rib space. The RP plane was developed by blunt dissection under the diaphragm and toward the psoas muscle till the visualization of the aorta. The costal margin was divided together with a 5-cm radial incision of the adjacent diaphragm (Figure 3). Abdominal contents were retracted to the right. The suprarenal aorta was accessed by the division of the left crus of the diaphragm. The left renal artery, superior mesenteric artery (SMA), and celiac trunk (CT) were dissected free and controlled with silastic loops (Figure 4). After heparinization, the aorta was clamped proximal to the CT, another clamp was placed proximal to the aortic bifurcation. Aneurysmal aorta was entered, balloon-tipped catheters were inserted to both renal arteries for the infusion of 500 mL cold

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Ringer solution to each of them. A 22-mm Dacron® graft was sutured to the aortic neck just distal to the orifice of the SMA with 4/0 polypropylene by using a strip of Teflon felt to buttress the anastomosis. The proximal clamp was moved to the graft to commence the perfusion of the visceral arteries. Ischemia of the visceral arteries was 26 min. The distal aortic anastomosis was performed in a similar fashion. Both clamps were removed to perfuse the lower body. The left and right renal artery buttons were prepared. The right renal artery was revascularized by using an 8-mm Dacron® interposition graft and the left renal artery was anastomosed directly to the aortic graft (Figure 5). The right and left renal ischemia duration were 77 and 99 min, respectively. A drain was placed to the RP space. The abdominal wall was closed as in a routine fashion. The diaphragm was repaired with interrupted polypropylene sutures. No chest tube was inserted. The air in the left pleural cavity was evacuated during the closure of the posterior muscle layers as the anesthesiologist hyperinflated the lungs.

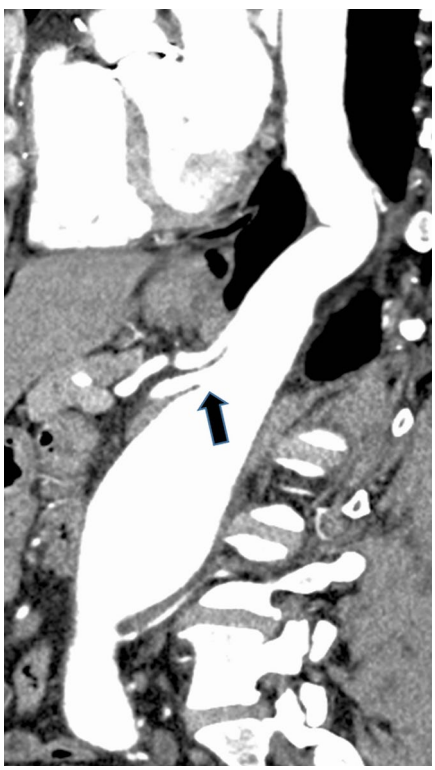

Figure 1. Sagittal computed tomographic image of the suprarenal abdominal aortic aneurysm. The arrow shows the superior mesenteric artery.

The patient tolerated the procedure well. The postoperative urine output was good and the creatinine level was 0.67 mg/dL. The patient did not receive

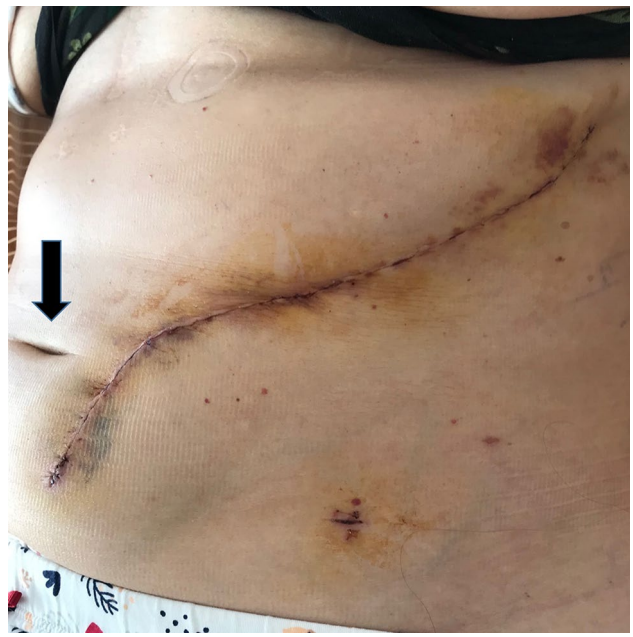

Figure 2. S-shaped incision from the left lateral edge of the rectus abdominis muscle at the umbilicus to the costal margin then to the ninth rib space. The arrow shows the umbilicus.

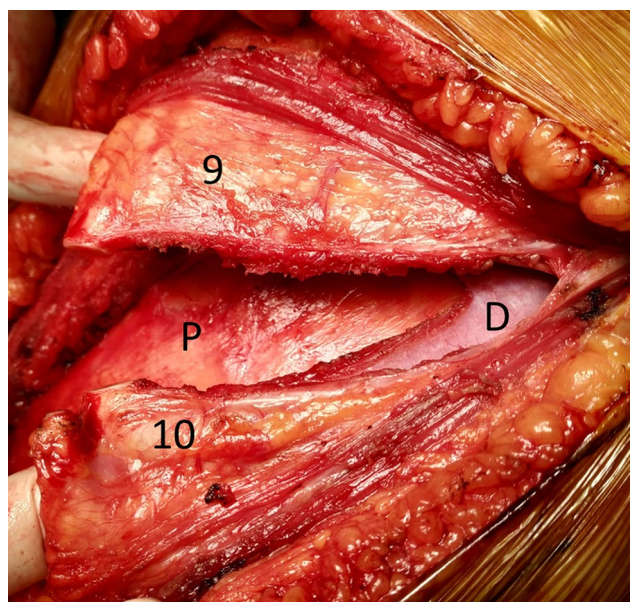

Figure 3. Intraoperative view (from the left) of the ninth rib space and radially divided diaphragm.
P: Peritoneum; D: Diaphragm.

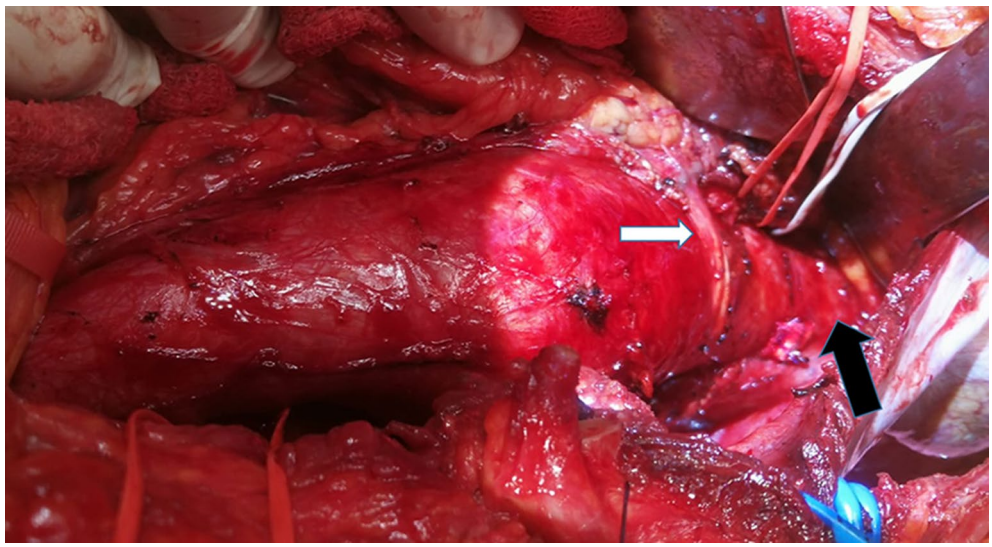

Figure 4. Intraoperative view of the aneurysmal aorta (from the left). Celiac trunk and superior mesenteric artery were looped with white and red silicone loops, respectively.
Black arrow: Clamp site. White arrow: Left renal artery.

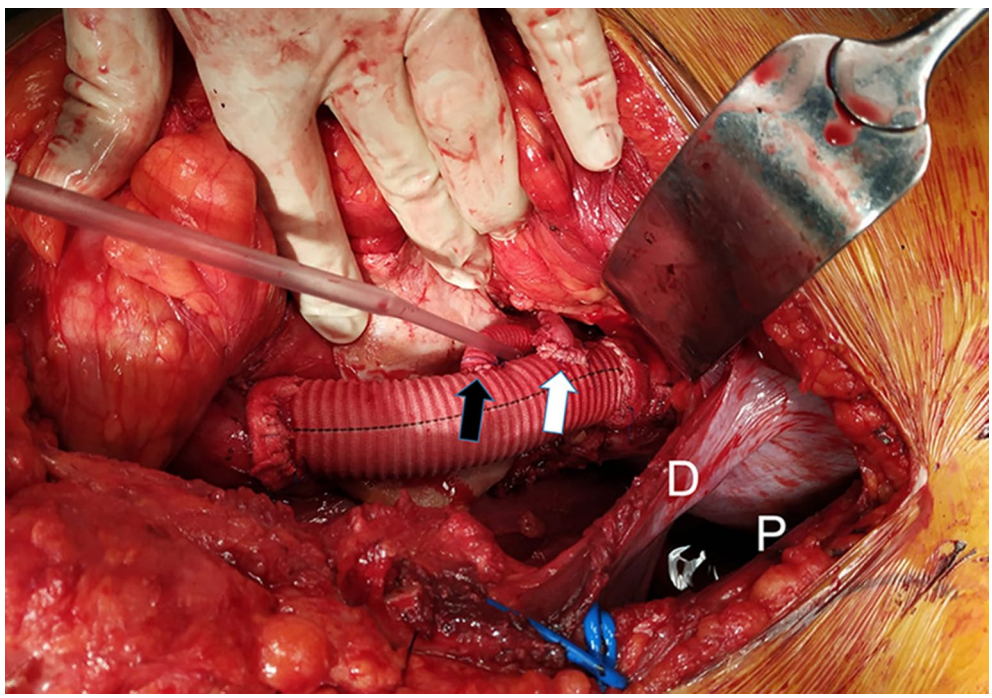

Figure 5. Intraoperative view of the aortic graft (from the left).
Black arrow: Dacron® graft to the right renal artery. White arrow: Direct anastomosis of the left renal artery to the aortic graft. D: Diaphragm, P: Pleural cavity.

any blood or blood products and was discharged five days after the operation. There was no complication related to the diaphragmatic incision. She remained asymptomatic and stable at her clinical follow-up appointment five months after the operation.

DISCUSSION

Suprarenal abdominal aorta is located in a compact anatomic region. It is surrounded by abdominal viscera anteriorly, vertebral column posteriorly and

diaphragmatic crux bilaterally. Either midline TP or lateral RP approaches can be used for the exposure of this region. The midline TP approach gives an excellent exposure of the infrarenal aorta and both iliac arteries and enables to place a supraceliac clamp at the diaphragmatic hiatus. The left renal vein, bowel mesentery, and pancreas lie anterior to the juxtarenal aorta. The left medial visceral rotation (the Mattox maneuver), which requires extensive dissection, is needed to expose the suprarenal aorta with the TP approach.[1]

The lateral RP incision provides unparalleled access to the abdominal aorta up to the supraceliac level, without entering the peritoneum and dissecting the other intraabdominal organs. The left renal and the left iliac arteries can be visualized directly. A hostile abdomen from multiple laparotomies, fatty omentum and bowel mesentery, pre-existing stomas, and redo aortic surgery after previous TP surgery do not constitute a problem. The incision involves fewer dermatomes than a midline incision, thereby reducing postoperative pain.[2] The fluid and temperature losses encountered by an open peritoneum are less with RP approach.[3]

The modifications of ninth intercostal incision have specific advantages other than the above-mentioned advantages of the RP approach.[2-4] Radial division of the diaphragm provides better exposure and increases the space available for clamp application to the suprarenal aorta.[3] This would also potentially facilitate the removal of suprarenal fixation wires of failed endovascular aneurysm repair grafts, when indicated.

Removal of segments of the rib, as in the 11th rib approach, to enter the retroperitoneum is not necessary and the underlying intercostal nerves remain covered which may result in less neuropraxic injury. The 11th rib approach requires a bigger incision on the wall of the chest and abdomen, as well as the resection of the two third of this rib. We have seen flank muscle denervation and bulging which resembled incisional hernia in patients who underwent 11th rib resection.

Renal protection by means of perfusion with cold crystalloid solutions was shown to be as effective as perfusion with cold blood.[5] Therefore, we used cold Ringer solution to perfuse both kidneys. Postoperative creatinine levels did not increase, despite relatively long renal ischemia.

True AAA in patients with Marfan syndrome is relatively rare and most AAAs in this disease are secondary to aortic dissection in the thoracic area.[6,7] Hagerty et al.[7] reported a case series of 12 Marfan patients with true AAA. In their report, by using a PubMed search, they found only eight case reports (including 13 patients) of AAA in patients with diagnosed or suspected Marfan syndrome from 1976 to 2009. Therefore, as of 2016, 25 cases were reported in the literature. As in our patient, these AAAs have a tendency to occur in relatively young patients[6] and the renal arteries were involved in about half of these aneurysms.[7]

The aortic root and thoracic aorta are typical sites for aneurysms in patients with Marfan syndrome. The outlook for patients with Marfan syndrome has improved due to better awareness and successful prophylactic root replacement for aneurysm disease.[8] Due to the increased longevity, periodic screening for AAA in Marfan patients who have undergone prior aortic root replacement or those with descending thoracic aortic disease was proposed.[7] Screening for AAA could include an abdominal sweep performed during the transthoracic echocardiogram.[9] Since there is no established consensus on endovascular repair for Marfan-related AAA, conventional graft replacement is accepted to be the gold standard.[6]

In conclusion, the RP approach with a limited thoracoabdominal incision through the ninth intercostal space is advantageous for the repair of AAAs involving the suprarenal aorta. This technique should be in the armamentarium of aortic surgeons, as they have to face with ever-increasingly difficult cases in the endovascular era.

Declaration of conflicting interests

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Cardiovascular Surgery and Interventions

Case Report Open Access

Intravenous cannula fracture in external jugular vein access: A case report

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ABSTRACT

External jugular vein (EJV) is commonly used for intravenous access, particularly in pediatric patients. A 2.5-year-old boy in whom an intravenous cannula fracture occurred was admitted. Since an intravenous access was difficult to establish due to previous attempts, intravenous access was established in the left EJV. The fracture of the cannula was noticed immediately after removal. After confirmation of the broken segment in subcutaneous tissue, it was surgically removed. In conclusion, training of the staff, good technique of insertion, proper care, attentive removal, early recognition and emergent removal of the fractured segment of the cannula are of utmost importance.

Keywords: Cannula, complication, equipment failure, jugular veins.

External jugular vein (EJV) is a commonly used site for intravenous access, particularly in pediatric patients.[1] To the best of our knowledge, although there is no consensus in the literature in regards to not using, or at least avoiding the use of EJV, the literature comprises occurrence of intravenous cannula fracture cases at the site of EJV.[2,3] Since the fracture of the tip of the cannula is a very rare complication, it can lead to intravenous migration, embolization, and thrombosis.[1-3] The issue of cannula fracture is a serious problem that must be undertaken and mandates proper diagnosis and treatment.[3] In this article, we present a pediatric case in whom an intravenous cannula fracture occurred at the site of EJV at the time of removal and was surgically removed.

CASE REPORT

A 2.5-year-old boy was diagnosed with extra-hepatic portal hypertension and was receiving treatment for esophageal varicose vein bleeding in the Pediatric Intensive Care Unit (PICU) for seven days. As active bleeding was brought under control, the central venous line was removed. Since it was difficult to establish an intravenous access in the upper and lower extremities due to too many attempts, the intravenous access was provided by an intravenous line inserted in the left EJV. As the patient was decided to be discharged from the hospital on Day 5 of the EJV access, the intravenous cannula at the EJV was removed by a nurse, who was aware that the half of the intra-corporeal part of the cannula was broken and remained in the subcutaneous tissue. The patient was consulted with the Pediatric Cardiovascular Surgery. On physical examination, the patient was hemodynamically stable. Palpation of the entrance site of the left EJV revealed a stiffness indicating that the fractured part of the cannula was still remaining within the subcutaneous tissue. Additionally, the EJV was wholly palpable throughout its course as a cord in the neck which suggested that the EJV was thrombosed. The first bedside evaluation with ultrasonography revealed the fractured part of the cannula within the EJV. Additionally, the EJV was thrombosed (Figure 1). The findings of the bedside ultrasonographic findings were confirmed by the consultant radiologist indicating that the broken part laid within the subcutaneous tissue extending into the thrombosed EJV lumen.

Following preoperative work-ups, the patient was transferred to the operation. Under intravenous sedation and local anesthesia, a small skin

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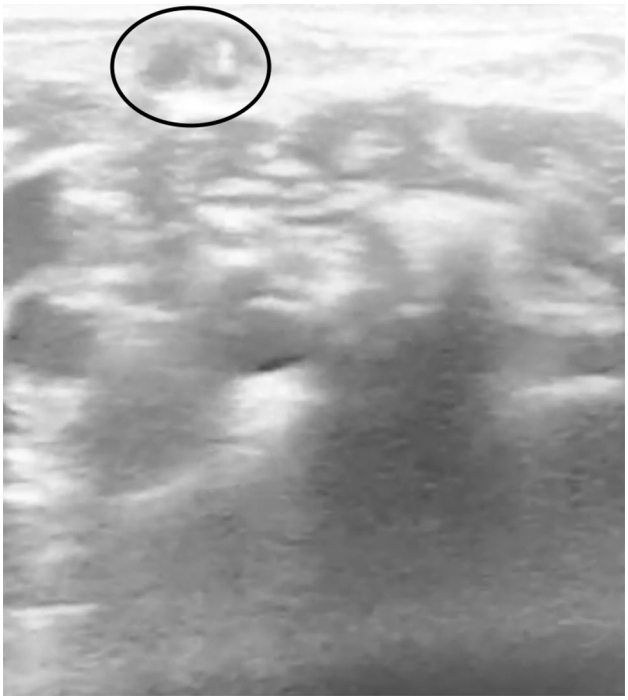

Figure 1. The ultrasonographic view of the external jugular vein and the fractured cannulas within the lumen of the vein.

incision was made at the entrance site. When the subcutaneous tissue was explored, the tip of the broken cannula coming out from the thrombosed EJV was found and removed (Figure 2). The EJV did not bleed after removal of the broken cannula, as it was totally thrombosed. The postoperative period was uneventful. An anticoagulant treatment was initiated with low-molecular-weight heparin with an anticipated duration of three months.

A written informed consent was obtained from the parents and/or legal guardians of the patient.

DISCUSSION

The intravenous cannulas are made of a variety of materials such as Teflon, polyurethane, polyvinyl chloride, or polyethylene. The complication rates seem to be lower in the cannulas made of Teflon and polyurethane than that of the others made of polyvinyl chloride and polyethylene.[4] The cannula in the current case was made of polyethylene, which is consistent with the literature. Additionally, along with the long-standing use of intravenous cannulas, low quality of the material used during fabrication and casualness at the time of removal of the cannula would be the reasons of the cannula fracture.[2]

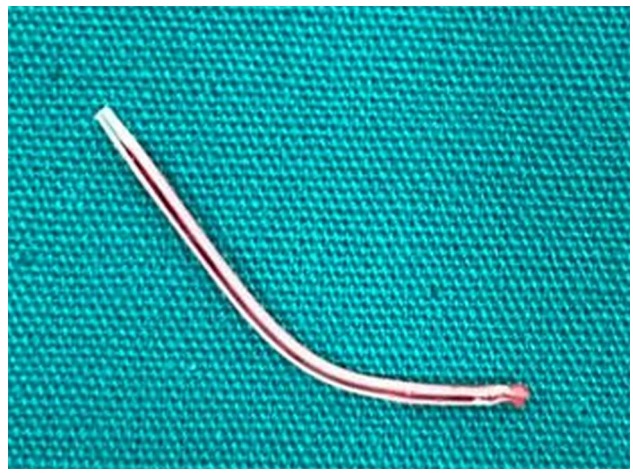

Figure 2. Intraoperative view of the removed fractured segment of the cannula.

Since the common outcomes of intravenous access are infection and thrombosis, migration, embolization of the fractured cannula is far less likely, which can lead to pulmonary embolism, arrhythmia, pulmonary vascular trauma, and myocardial infarction.[5] None of these complications occurred in the current case, as it was highly likely that the EJV was already thrombosed at the time of the removal of cannula, preventing migration and embolization of the cannula to distance organs.

External jugular vein is used as an intravenous access line, particularly more common in pediatric patients than adults, mainly due to the difficulty in establishing extremity intravenous access and in the situations where emergent volume replacement and resuscitation are necessary.[2,3] In our opinion, the EJV is located at a mobile site of our body, the neck. Additionally, it is difficult to stabilize the intravenous line in place at the neck, and it necessitates a constant observation by a companion or the nurse. Moreover, the cannulas placed at the mobile sites are subject to be exposed to a constant wrench and upturn, which, in our opinion, is the main mechanism that weakens and eventually results in fracture of the cannula. The cases of cannula fractures are more common among the patients in whom the cannula is placed at a mobile site vein, such as the neck, wrist and cubital region.[2,3,6]

Overall, due to the aforementioned reasons, the caregivers should be more careful in regards to the intravenous access line fracture. Application of a

gentler force of withdraw would be beneficial at the time of removal. Furthermore, it is reasonable to observe the tip of the cannula immediately after withdrawal, as many of the complications are related to the unawareness of a fractured cannula.[2,3,5] In our opinion, along with the application of cannulas at a mobile site, the intravenous part of the cannula be made of a stiffer material, insufficient stabilization, insertion of a large cannula in a small vein (vein-cannula mismatch) are the other contributing factors that expedite fracture of the cannula.

In conclusion, the whole medical staff, particularly the nurses, should be aware of this rare, but potentially risky complication with the use of intravenous cannulas. However, training of the staff, good technique of insertion, proper care, an attentive removal, early recognition and emergent removal of the fractured segment of the cannula are of utmost importance to prevent high-risk, fractured cannula-related complications.

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Cardiovascular Surgery and Interventions

Case Report Open Access

Surgical retrieval of an embolized Amplatzer™ ductal occluder device with review of comparable cases

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ABSTRACT

Well-known complications of transcatheter shunt closure interventions are embolizations of devices. The initial procedure after embolization of a device is transcatheter interventions such as repositioning or retrieval with a sheath, bioptome or a snare. In some cases, surgical procedures may require and be privileged to reduce the harm to the patient. In this article, we report an eight-year-old boy who underwent surgical retrieval of Amplatzer™ Duct Occluder I device from the left pulmonary artery without cardiopulmonary bypass and discuss the safe retrieval techniques of commonly used devices.

Keywords: Catheter complications, device embolization, ductal occluder, surgical retrieval.

In recent years, interventional transcatheter device closure has become the most favorite treatment modality in congenital heart diseases. However, it can occasionally lead to catastrophic complications such as embolization. Although transcatheter retrieval is the first choice, surgical techniques may be inevitable in some cases. Herein, we report a surgical retrieval procedure of an embolized Amplatzer™ duct occluder (ADO) (Abbott Structural Heart, Plymouth, MN, USA) from the left pulmonary artery without cardiopulmonary bypass in the light of literature review.

CASE REPORT

An eight-year-old male patient with a known patent ductus arteriosus (PDA) was admitted for percutaneous device closure. Echocardiography revealed a tubular PDA 6.4 mm in diameter and 21 mm in length, with moderate pulmonary hypertension and left ventricular dilatation. He underwent right heart catheterization which identified a 10-mm PDA. The hemodynamic data showed a mean pulmonary artery pressure of 34 mmHg, with a mean aortic pressure of 55 mmHg. The Qp/Qs ratio was 2.89 and Rp/Rs ratio was 0.09. Balloon occlusion showed a drop in pulmonary pressures to half of systemic and a 12×10 mm ADO I device (Abbott Structural Heart, Plymouth, MN, USA) was positioned with success. Within few hours of deployment, control telecardiogram and echocardiography revealed that the device was embolized into the left pulmonary artery (Figure 1). The initial plan was to retrieve the device angiographically with percutaneous technique. Several attempts with 5Fr Judkins and 5Fr Multipurpose catheters failed.

The patient was immediately transferred to the operating room. Median sternotomy was performed. He was hemodynamically stable. Aorta, pulmonary artery, and PDA were dissected. The device was fell in the left pulmonary artery. The distal end was controlled with snares and occluded, and the proximal part of left pulmonary artery was cross-clamped and an arteriotomy over the device was performed. We removed the device successfully without any complication. The PDA was ligated with the Ethibond® suture and transfixed. The pulmonary artery was primarily repaired using 5-0 prolene sutures. After the operation, the patient was

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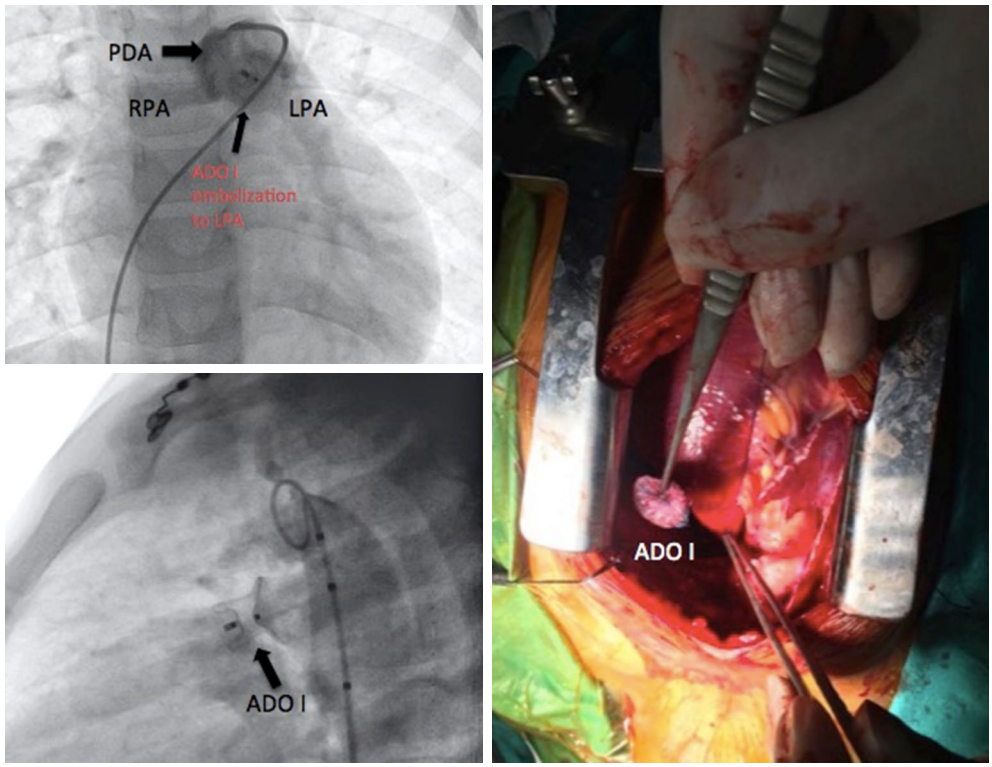

Figure 1. Angiographical and intraoperative images showing embolized device.

transferred to cardiac intensive care unit, extubated within few hours, and discharged home on the third postoperative day with full recovery. Follow-up echocardiogram showed no flow across the ductus arteriosus, no residual defect, and no peripheral pulmonary arterial stenosis. A written informed consent was obtained from the parents and/or legal guardians of the patient.

DISCUSSION

Transcatheter PDA closure was first applied in 1967 and the procedure became more practical. There have been many dramatic improvements and, over the last two decades, transcatheter approaches has become the considerable.[1]

Anatomical varieties, calcification and aneurysm formation, left ventricular dysfunction and pulmonary hypertension may complicate transcatheter closure of PDA.[2]

Currently, in most age groups, except premature infants, transcatheter therapy for persistent flow through the arterial duct is accepted as a well-established alternative. The design of occluder devices has been improved regarding the occlusion rate, stability, and smaller sizes of delivery systems. The initial ADO can accomplish high rates of occlusion with minimum complications in different sizes and morphology of ducts and age groups.[3]

There are several factors which affect the performance of transcatheter device closure of PDA such as vascular accessibility, anatomical structure of the ductus, and selecting optimal device. The ADO II devices (Abbott Structural Heart, Plymouth, MN, USA) are the proper for retrograde aortic approach. Small-sized ducts are convenient for coils, and occluders are usually used for larger ones.[4]

Severe complications such as embolization, infection, hemolysis, protrusion into aorta or pulmonary artery causing obstruction or narrowing, spontaneous recanalization and post-procedure left ventricular systolic dysfunction have been defined after percutaneous techniques.[5,6]

The role of all transcatheter closure procedures of intracardiac and extracardiac shunts has gained

Table 1
Review of the literature on surgical retrieval of embolized devices

No	Author	Year	Patient age	Sex	Diagnosis	Embolized device and size (mm)	Embolization site	Surgical retrieval technique
1	Verma et al.[14]	2003	10 years	Female	ASD	ASO (14 mm) (AGA Medical Corp., Golden Valley, Minnesota, USA)	Left ventricle	Median sternotomy, with CPB
2	McMullan et al.[11]	2007	11.5 months		PDA	ADO (6-4 mm) (AGA Medical Corp., Golden Valley, Minnesota, USA)	Descending aorta	Left posterolateral thoracotomy, without CBP
3	Misra et al.[15]	2007	18 years	Male	ASD	Blockaid septal occluder device (28 mm) (Alloy Comp, Shangai, China)	Pulmonary artery	Median sternotomy, with CPB
4	Aydin and Ozisik[16]	2009	4 months	Female	PDA	Transcatheter coil (Ductocclud, PPM coil, PFM AG, Cologne, Germany)	Left pulmonary artery	Left thoracotomy, without CPB
5	Amanullah et al.[17]	2011	16 years 53 years 6 months 4 years	Female Female Male Female	ASD ASD PDA PDA	ASO (36 mm) ASO ADO (4-6 mm) Amplatzer muscular ventricular septal defect occluder (12 mm)	Right ventricle Ascending aorta Descending aorta Right pulmonary artery	Sternotomy, with CPB Sternotomy, with CPB Left thoracotomy, without CPB Sternotomy, with CPB
6	Yuce et al.[18]	2011	44 years	Male	ASD	ASO (26 mm) (AGA Medical Corp., Golden Valley, Minnesota, USA)	Right ventricle	Median sternotomy, with CPB
7	Gokaslan et al.[13]	2012	4 years 8 years 9 years 15 years 15 years 9 years 8 years 2 years 10 years		ASD ASD ASD ASD ASD ASD PDA PDA Muscular VSD	ASO (38-34 mm) ASO (32-36 mm) ASO (36-40 mm) ASO (29-33 mm) ASO (38-42 mm) Biostar BSR-28 ADO (10-8 mm) Amplatzer Nit. Ocluder (9-6) Amplatzer VSDmusc (16 mm)	Tricuspid valve Right ventricle Left ventricle Pulmonary valve Right atrium Tricuspid valve Ascending aorta Tricuspid valve Tricuspid valve	Sternotomy, with CBP
8	Son and Park[19]	2012	45 years	Female	ASD	ASO (32 mm)	Right pulmonary artery	Median sternotomy, with CPB
9	Tai et al.[20]	2014	22 years		VSD	HeartR membVSD Occl.(4)	Iliac artery	Laparatomy
10	Cianciulli et al.[21]	2014	66 years	Male	ASD	ASO (22 mm)	Left ventricle	Median sternotomy, with CPB
11	Tang et al.[22]	2014	12 months	Female	PDA	ADO (6-8 mm)	Descending aorta	Posterolateral thoracotomy
12	Gumus et al.[23]	2014	5 years	Female	PDA	ADO (6-8 mm)	Abdominal aorta	Laparatomy
13	Celik et al.[24]	2016	35 years	Female	ASD	ASO (13.5 mm) (Occlutech Figulla Flex II)	Abdominal aorta	Laparatomy
14	Nath and Pandit[25]	2016	48 years	Female	ASD	ASO (30 mm)	Right ventricle	Median sternotomy, with CPB
15	Davies et al.[26]	2017	58 years	Male	PFO	Amplatzer fenestrated ASO (30 mm)	Visceral abdominal aorta	Laparotomy
16	Kumar et al.[27]	2017	11 years	Male	Coronary-cameral fistula (RCA to RV)	Amplatzer vascular plug (10×7 mm)	Left pulmonary artery	Median sternotomy, with CPB
17	Georgiev et al.[28]	2018	24 years 25 years	Female Female	ASD ASD	ASO (28 mm) Occlutech (28 mm)	LVOT PA	Median sternotomy, with CPB Median sternotomy, with CPB
18	Şişli and Epçaçan[29]	2019	11 months	Female	PDA	ADO II (5/4 mm) (St.Jude Medical Corp., Plymouth, MN, USA)	Right common iliac artery	Laparatomy, PTFE tube graft interposition
19	Sun et al.[30]	2020	2 years	Male	PDA	ADO	Bulged out of descending aorta (Iatrogenic CoA)	Posterolateral thoracotomy, with CPB

ASD: Atrial septal defect; PDA: Patent ductus arteriosus; VSD: Ventricular septal defect; PFO: Patent foramen ovale.

importance in recent years as PDA closure. These procedures eliminate the need for sternotomy and cardiopulmonary bypass and shortens the length of hospital stay.[7] Although percutaneous techniques become popular due to less mortality and morbidity rates and early discharge from hospital, they are not free of complications. Device embolizations in different sites of circulatory system may cause life-threatening damages. In the literature, device embolization rates were 4% in 1991, 20% in 1996, and 0.55% in 2005.[8,9] New generation devices significantly decreased serious complications.[8,9] However, embolized devices which require urgent surgical management are still reported and majority of these are case reports.[10,11]

In the literature, from 72 embolization cases between years 2000 and 2020, 40 of them were atrial septal defects, 17 were PDA, nine were ventricular septal defects, three were patent foramen ovale with neurological symptoms and signs, one was mitral paravalvular leak, one was coronary-cameral fistula, and one was ascending aorta pseudoaneurysm. The most frequently embolization site of the device was pulmonary artery, similar to our case. In the relevant literature, device removal or repositioning was achieved mostly through the percutaneous route. A total of 49 of 71 cases were rescued via transcatheter techniques. Twenty-three patients underwent surgical procedure. All embolized devices were successfully retrieved both surgically and angiographically (Table 1).

In hemodynamically stable cases, the first choice is to attempt percutaneous rescue methods. The retrieval of an embolized device from the pulmonary artery by snaring technique has been described and there are various reports regarding the successful retrieval devices either by surgery, a percutaneous method using various snares or bioptomes, or by a sheath in the sheath technique.[12,13]

After device embolization, the main goal is to localize the embolized device into a harmless position. Operators using transcatheter occluder devices should be familiar with performing percutaneous retrieval techniques. However, in life-threatening cases, it should not be late for recognition and surgical intervention. It is also important to consider late embolization of devices and close follow-up with X-ray and control echocardiograms to realize earlier. The literature strongly suggests that these devices should be only inserted in facilities, where back-up of pediatric cardiovascular surgical cover, operating room, and blood product preparations are immediately available. Although the embolizations seem to be rare, the results may be destructive such as extremity loss, mortality or, at least in the best-case scenario, recurrent surgical and/or endovascular interventions may be required.[14]

In conclusion, although transcatheter closure is applicable and advantageous even in the lowest weight infants, there are absolutely many serious catheterization-related risks, as the patient size becomes smaller. Further improvements would advance the safety and utility of transcatheter procedures.

Declaration of conflicting interests

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Cardiovascular Surgery and Interventions

Letter to the Editor Open Access

Roemheld syndrome: Apprehending arrhythmia in a different perspective

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An intriguing article by Bodur et al.[1] investigated the association between premature atrial contractions (PACs) and gastroesophageal reflux disease (GERD). The authors found that esophagitis and/or gastritis in patients with GERD symptoms were independently associated with the increased prevalence and number of PACs. The exact mechanism of esophagitis and/or gastritis-induced supraventricular arrhythmia is still unclear. However, several hypotheses have been proposed as the underlying pathomechanism discussed by the authors, including alteration in vagal and sympathetic balance and left atrium mechanical stimulation by esophageal distension.

Arrhythmias, particularly supraventricular arrhythmias, can be caused by several predisposing factors, including gastrointestinal problems. Roemheld syndrome, known as gastrocardiac syndrome, an overlap and link between the gastrointestinal symptoms and arrhythmias, was first observed by Ludwig Roemheld[2] later, several subsequent reports described this syndrome.

Finding the link and accurately diagnosing this syndrome is often difficult due to contributions from various possible mechanisms that may cause this syndrome, including vigorous exercise, inflammation within adjacent positioning of esophagus and atria, autoimmune disorders, common nerve innervations, impediments in coronary blood flow, and hiatal hernias.[2] Esophagus stimulation, whether mechanical or chemical by acid reflux, potentiates afferent vagal activity in GERD concomitant arrhythmia patients. Elevated vagal tone shortens effective atrial refractoriness, resulting in development of atrial arrhythmia.[3]

In addition, GERD may release various inflammatory cytokines, i.e., interleukin (IL)-1β and IL-6, which lead to systemic inflammation. The increase of circulating cytokines may prompt arrhythmia development, particularly atrial fibrillation (AF). In addition, acid reflux may cause lower esophagus inflammation and subsequently penetrate the esophagus wall, affecting the vagal nerves and leading to atrial myocarditis or local pericarditis.[2,3] This may happen due to adjacency of esophageal to atrium and alteration of local receptors. Consequently, cardiac rhythm afferent-efferent reflex mechanisms were induced, secondary to vagal nerve stimulation, thus inducing arrhythmia.[2]

The presence of hiatal hernia can also directly compress atrium, causing a decrease in blood supply to the heart, resulting in relative ischemia that can lead to arrhythmias. This hiatal hernia can also aggravate acid reflux in GERD.[2,3]

Esophageal acid exposure also has potential impact on coronary blood flow. It has been reported that coronary flow was reduced by acid instillation into esophagus. This phenomenon is mediated by autonomic reflex and postulated as one of leading causes of syndrome X, characterized by typical angina despite normal coronary arteries. This phenomenon is absent in denervated heart transplant recipients, supporting that reduced coronary blood flow is achieved through cardioesophageal reflex.[4]

As the first line GERD therapy, proton pump inhibitors (PPIs) may hold potential therapeutic effects in this situation. The PPIs have multimodal effects

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beyond acid suppression mediated by proton pump (K^+-H^+ ATPase) inhibition, including antioxidant and anti-inflammatory properties. They have potential antiarrhythmic and cardioprotective agent properties due to functional similarity proteins of the gastric K^+-H^+ ATPase within cardiac.[2,3]

Quinidine and disopyramide, antiarrhythmics with vagolytic properties,[5] can be used when arrhythmia is suspected due to vasovagal stimulation, while simultaneously treating the underlying gastrointestinal disease.

In conclusion, various pathophysiological mechanisms that may underlie the occurrence of arrhythmias in Roemheld syndrome should be investigated in patients presenting with gastrointestinal complaints and arrhythmias.

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