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Late surgical conversion after failed endovascular aortic repair: Our single-institutional experience

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ABSTRACT

Objectives: In this study, we report our single-center experience with late surgical conversion (SC) after endovascular aneurysm repair (EVAR) and risk factors for reintervention.

Patients and methods: Between January 2007 and December 2017, a total of 98 patients (94 males, 4 females; mean age: 69.1±8.6 years; range, 35 to 86 years) who underwent infrarenal EVAR were retrospectively analyzed. During the study period, additional eight patients who underwent EVAR at an external center were referred to our center. Overall, nine patients underwent late SC. In the late SC group, stent grafts used for EVAR were Endurant™ (n=5), Talent™ (n=2), Powerlink™, and Anaconda™ (n=1).

Results: The mean time from initial EVAR to open conversion was 45.3±35.4 months. Four (44.4%) patients presented with more than one different concomitant indications. The most frequent reason for the late SC was type 3 endoleak (n=5, 55.5%). Late SC was performed electively in five (55.5%) patients. Partial stent graft removal was performed in three (33.3%), complete removal in three (33.3%), and complete preservation of the stent graft in three (33.3%) patients. Among 98 patients, the mean aneurysm diameter was significantly higher in those with late complication and undergoing second EVAR (p=0.001). The cut-off value for second EVAR was ≥66 mm with a sensitivity of 88.89% and specificity of 71.91% (p=0.001).

Conclusion: The surveillance program after EVAR is of utmost importance to ensure that patients do not need urgent conversion, particularly in patients with an initial aneurysm diameter of ≥66 mm.

Keywords: Abdominal aorta aneurysm, complication, endovascular aneurysm repair, late surgical conversion.

Endovascular aneurysm repair (EVAR) has revolutionized the management of infrarenal abdominal aortic aneurysms (AAAs), since the first successful intervention two decades ago.[1] Advances in endovascular stent technology, increasing experience and technical skills have resulted in EVAR becoming the treatment of choice for more than half of patients in many referral centers.[2]

Despite the benefits of EVAR compared to the open surgery, such as significantly lower short-term mortality, shorter hospitalization, more rapid recovery and less pain, the long-term durability of EVAR still remains as a concern. It is also associated with increased rates of reintervention to treat endoleak, graft rupture, stent fractures, graft thrombosis and infection with longer follow-up time.[3] The majority of these complications can be successfully managed with endovascular interventions; however surgical conversion (SC) is still required in 0 to 9% of cases as a last resort in the management of complications refractory to endovascular intervention.[4,5] Surgical conversion after EVAR is technically more challenging compared to primary open repair and is associated with remarkably high mortality rates in emergency patients, ranging between 20 and 40%.[6] However, mortality rates in elective SCs are more reasonable, similar to primary open repair.[7]

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In the present study, we report our single-center experience with late SCs after EVAR, to evaluate the current indications, surgical strategy, and clinical course for conversion, and to identify possible risk factors for reintervention.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Dr. Siyami Ersek Chest Heart and Vascular Surgery Training and Research Hospital, Department of Cardiovascular Surgery between January 2007 and December 2017. Data of patients who underwent infrarenal EVAR and late SC after previous EVAR during the study period were screened. Data of patients who underwent late SC at our center after an index EVAR procedure performed at an external institution were also reviewed. Finally, a total of 98 patients (94 males, 4 females; mean age: 69.1±8.6 years; range, 35 to 86 years) who underwent infrarenal EVAR were included. During the study period, additional eight patients who underwent EVAR at an external center due to sac enlargement or graft thrombosis after failed EVAR were referred to our center. Overall, nine patients underwent late SC. Patients' demographic, anatomic, operative, and postoperative data were retrieved from the hospital database. Missing surveillance data were completed using the dataset records for the Republic of Türkiye, General Directorate of Civil Registration and Nationality.

The late SC was defined as a surgical reintervention performed at least 30 days after the initial EVAR. The 30-day cut-off was determined to exclude the cases, if the conversion was performed on time or within first 30 days of the initial EVAR. The EVAR device brand, pre-EVAR aneurysm diameter, EVAR configuration (bifurcated, aortouniiliac), indication for SC, interval between initial EVAR and late SC, intraoperative data, length of hospital and intensive care unit (ICU) stay, postoperative complications, operative mortality, 30-day mortality, and long-term mortality were noted. Intraoperative data included surgical approach (transperitoneal or retroperitoneal), the SC technique (stent graft removal; complete/partial or not), position and duration of aortic cross-clamping, type of reconstruction, estimated blood loss, and operative time. The physical status of all patients was evaluated preoperatively using the American Society of Anesthesiologists (ASA) score.

All patients underwent ultrasound imaging and computed tomography angiography (CTA) surveillance at one, six, and 12 months and, then, annually as the post-EVAR follow-up protocol at our institution. The late SCs were performed either in the elective and emergency setting. Emergency SCs were performed for patients with painful or ruptured aneurysms. In our clinical practice, SC was performed as a last resort for the cases in whom endovascular reintervention was not feasible. The patients with rupture in the emergency setting preferably underwent late SC. Preoperative CTA scan was performed in all patients undergoing late SC.

Statistical analysis

Statistical analysis was performed using the Number Cruncher Statistical System (NCSS) version 2007 software (NCSS LLC, Kaysville, UT, USA). Continuous variables were presented in mean ± standard deviation (SD), while categorical variables were presented in number and frequency. The Mann-Whitney U test was used to compare the differences between two independent groups, when the dependent variable was ordinal or continuous, but not normally distributed. The Student t-test was used for groups with normal distribution. The Pearson correlation analysis was used to examine the relationships between variables. The Pearson chi-square test, Fisher-Freeman-Halton test, and Fisher exact test were used to compare the qualitative data. The receiver operating characteristic (ROC) curve was used to obtain a cut-off value to predict the need for a second intervention. A p value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Demographic and preoperative characteristics of patients who underwent late SC are summarized in Table 1.

Aneurysm characteristics

The mean initial AAA diameter of the patients was 62.1±8.6 mm. The mean aneurysm diameter was significantly higher in patients undergoing second EVAR (p=0.001) (Table 2). Therefore, a cut-off value regarding the initial diameter of the aneurysm sac was determined to predict the need for a second intervention or subsequent SC. The ROC curve analysis and diagnostic scan tests are shown in

Table 1
Baseline characteristics of patients (n=9)

	n	%	Mean±SD	Range
Age (year)			69.1±8.8	59-85
Sex				
Male	8			
Female	1			
Late SC				
Emergency	4	44.4		
Elective	5	55.5		
ASA class				
III	6	66.6		
IV	3	33.3		
Indications for late SC				
Endoleak type 1a	2	22.2		
Endoleak type 3	5	55.5		
Rupture	3	33.3		
Graft thrombosis	2	22.2		
Migration	3	33.3		

SD: Standard deviation; SC: Surgical conversion; ASA: American Society of Anesthesiologists.

Table 2
Comparisons of aneurysm diameters

		Aneurysm diameter			
	n	Mean±SD	Median	Min-Max	*p*
Late complication					
No	69	60.87±7.68	60	45-81	t:-2.105
Yes	29	65.31±10.21	68	45-87	0.041*†
Second EVAR					
No	89	61.02±7.95	60	45-81	Z:-3.896
Yes	9	73.67±7.66	71	63-87	0.001**‡
Surgical conversion					
No	97	61.93±8.36	61	45-82	-
Yes	1	87.00±0	87	87-87	-

EVAR: Endovascular aneurysm repair; SD: Standard deviation; † Student-t test; ‡ Mann-Whitney U test; * p<0.05; ** p<0.01.

Table 3
Diagnostic scan tests for aneurysm diameter and ROC curve results

	Diagnostic scan					ROC Curve		
	Cut-off	Sensitivity	Specificity	PPV	NPV	Area	95% CI	*p*
Late complication	≥66	55.17	75.36	48.48	80.00	0.645	0.514-0.775	0.024*
Second EVAR	≥66	88.89	71.91	24.24	98.46	0.895	0.813-0.976	0.001**

ROC: Receiver operating characteristics; EVAR: Endovascular aneurysm repair; PPV: Positive predictive value; NPV: Negative predictive value; * p<0.05; ** p<0.01.

Table 3. The cut-off value for the second EVAR was ≥66 mm with a sensitivity of 88.89%, specificity of 71.91%, positive predictive value (PPV) of 24.24%, and negative predictive value (NPV) of 98.246% (p=0.001). In the ROC analysis, the area under the curve (AUC) was determined as 89.5% (Figure 1).

Initial endovascular intervention characteristics in late SC group

All initial EVARs were performed electively due to AAAs. The mean aneurysm diameter before EVAR was 76±7.4 mm. The mean time from initial EVAR to open conversion was 45.3±35.4 months. Initially implanted endovascular grafts that required conversion included Endurant™ (Medtronic Inc., CA, USA) in five (55.5%), Talent™ (Medtronic, CA, USA) in two (22.2%), Anaconda™ (TERUMO Corp., MI, USA) in one (11.1%), and Powerlink™ (Endologix LLC, CA, USA) in one (11.1%) patient. Endovascular reinterventions were attempted in four (44.4%) patients as a salvage procedure before subsequent conversion.

Indications for late SCs

Four (44.4%) patients had more than one different indication for the late SC. The most frequent reason was type 3 endoleak with aneurysm sac expansion (n=5, 55.5%), followed by graft migration with sac expansion (n=3, 33.3%) and rupture (n=3, 33.3%). No endoleak was observed in three patients.

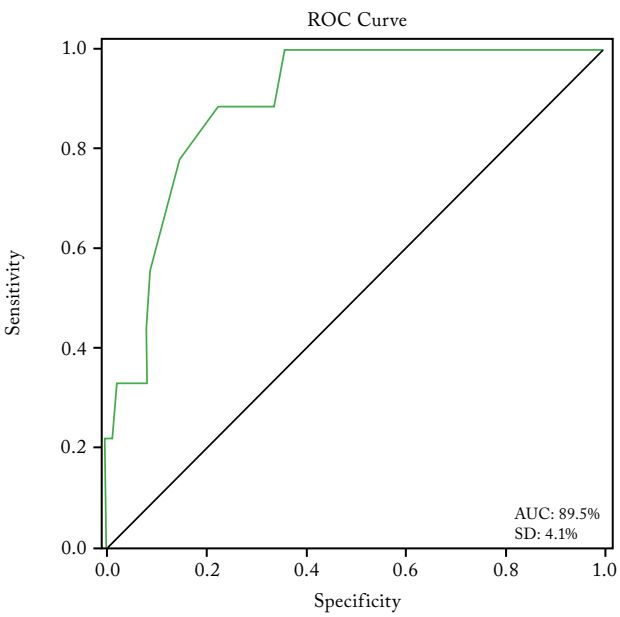

Figure 1. A ROC curve analysis for a cut-off value regarding the initial diameter of the aneurysm sac was determined to predict the need for a second intervention or subsequent surgical conversion.

ROC: Receiver operating characteristics; AUC: Area under the curve.

Late SC was performed electively in five (55.5%) patients and emergent surgery was applied in the remaining four patients. The emergency group included three patients with rupture and one patient with painful sac enlargement and graft migration.

In the elective group, indications for the late SCs were proximal type 1 endoleak (n=2), type 3 endoleak (n=2), graft migration (n=1), and graft thrombosis (n=2); one of them presented with main body occlusion and the other with left iliac limb occlusion. The details for the late SC for each individual case are summarized in Table 4.

Surgical procedure

The surgical approach included a midline transperitoneal approach in seven (77.7%), patients and extra-anatomic axillofemoral bypass (n=1, 11.1%) and cross-femoral bypass (n=1, 11.1%). Operative details are shown in Table 5.

The abdominal aorta was cross-clamped suprarenally in four (44.4%) patients and infrarenally in two (22.2%) patients, and the thoracic aorta was cross-clamped to provide emergency proximal aortic control in one hemodynamically unstable patient (11.1%) who presented with a ruptured aneurysm.

The aortic cross-clamp was gradually shifted distally in all patients who underwent suprarenal aortic cross-clamping during aortic reconstruction to reduce visceral and renal ischemic time. The proximal aortic cross-clamping was not performed in two cases undergoing extra-anatomic bypass grafting. The mean duration of the aortic cross-clamping was 24.5±11.1 min. Distal arterial control was achieved by cross-clamping of iliac arteries below the stent graft in five patients and at the stent graft level in two patients in whom further iliac exposure was not feasible.

After the aneurysm sac was opened, back-bleeding lumbar arteries were oversewn. In three (33.3%) patients, the proximal and distal end of the stent graft were well incorporated into the aortic wall. Partial stent graft removal was performed to reduce the risk of intraoperative injury to the aortic wall and to reduce aortic cross-clamping level, as well as the procedure time as previously described in detail

Table 4
Details for late SC after EVAR

Patient	Age (year)	AAA (pre-EVAR) diameter (mm)	Type of the stent graft	Indication for conversion	Emergency Status	Interval to conversion (month)	Explantation of stent graft	Operative details	Complications
1	70	72	Endurant	Endoleak type 3/ migraton/ rupture	Emergency	60	Partial	Aortic reconstruction with remnant stent grafts, Aorto-biliac bypass using bifurcated Dacron graft	The patient undergoing SC was hemodynamically unstable on admission, and died during operation
2	74	82	Talent	Rupture	Emergency	60	Complete	Aorto-biliac bypass using bifurcated Dacron graft	The patient presenting with rupture died due to acute renal failure and pulmonary complications in ICU
3	60	65	Anaconda	Graft thrombosis	Elective	5	Total preservation	Axillobifemoral bypass	None
4	60	68	Endurant	Endoleak type 1a/type 3	Emergency	62	Complete	Aorto-biliac bypass using bifurcated Dacron graft	Required temporary renal dialysis and reoperation for abdominal wound dehiscence
5	59	80	Endurat	Endoleak type 3/ migration	Elective	12	Partial	Aortic reconstruction with remnant stent grafts, Aorto-bifemoral bypass using bifurcated Dacron graft	None
6	65	68	Powerlink	Graft thrombosis	Elective	24	Total preservation	Cross-femoral bypass	None
7	81	87	Edurant	Endoleak 1a	Elective	5	Complete	Aorto-biliac bypass using bifurcated Dacron graft	None
8	68	78	Talent	Endoleak type 3/migration	Elective	60	Partial	Aortic reconstruction with remnant stent grafts, Aorto-biliac bypass using bifurcated Dacron graft	None
9	85	84	Endurant	Endoleak type 3/rupture	Emergency	120	Total preservation	Treated by nonabsorbable mass sutures with three pairs of PTFE felt pledgets	None

SC: Surgical conversion; EVAR: Endovascular aneurysm repair; AAA: Abdominal aortic aneurysm; ICU: Intensive care unit; PTFE: Polytetrafluoroethylene.

Table 5
Operative details of patients undergoing late SC (n=9)

	n	%	Mean±SD	Median	Min-Max
Interval to conversion (month)			45.33±37.61	60	5-120
Emergency status					
No	5	55.6			
Yes	4	44.4			
Approach					
Transperitoneal	7	77.8			
Extraanatomic	2	22.2			
Location of aortic cross-clamping					
None	2	22.2			
Suprarenal	4	44.4			
Infrarenal	2	22.2			
Thoracic	1	11.1			
Stent graft explantation					
Partial	3	33.3			
Total	3	33.3			
Total preservation	3	33.3			
Cross-clamping time (min)			24.57±11.99	20	0-45
Operative time (min)			214.78±47.53	220	120-284
Operative blood loss (mL)			550.00±250.00	600	150-850
Operative mortality					
No	8	88.9			
Yes	1	11.1			
Long-term mortality					
No	7	100.0			
Yes	0	0.0			
30-Day mortality					
No	7	77.8			
Yes	2	22.2			

SC: Surgical conversion; SD: Standard deviation.

elsewhere (Figure 2b).[8] However, no significant difference was found in the preference for stent graft removal options in terms of hospital mortality (Table 6). The indication for surgery in these three patients was type 3 endoleak with graft migration, and one of them also had a rupture. Aortobiiliac (n=2) and aortofemoral (n=1) bypass were performed with a bifurcated Dacron® graft as the surgical option.

Three (33.3%) patients, two of them with type 1 endoleak and one with rupture, required complete stent graft removal. In these patients, prosthetic aortic reconstruction using a bifurcated Dacron® graft was performed as aortobiliac bypass (Figure 2a).

Finally, the stents grafts were completely preserved in three of all nine patients. One of them showed rupture due to a tear in the fabric of the endovascular stent, which could be treated with three pairs of polytetrafluoroethylene (PTFE) felt pledgets and non-absorbable mass sutures. Axillobifemoral bypass was performed in one of the patients with total thrombotic occlusion of the stent graft. Patient No. 9 underwent cross-femoral bypass due to occlusion of left iliac limb of the stent graft (Figure 2c). In these three patients, complete preservation of the stent graft was achieved, reducing the risk of possible SC.

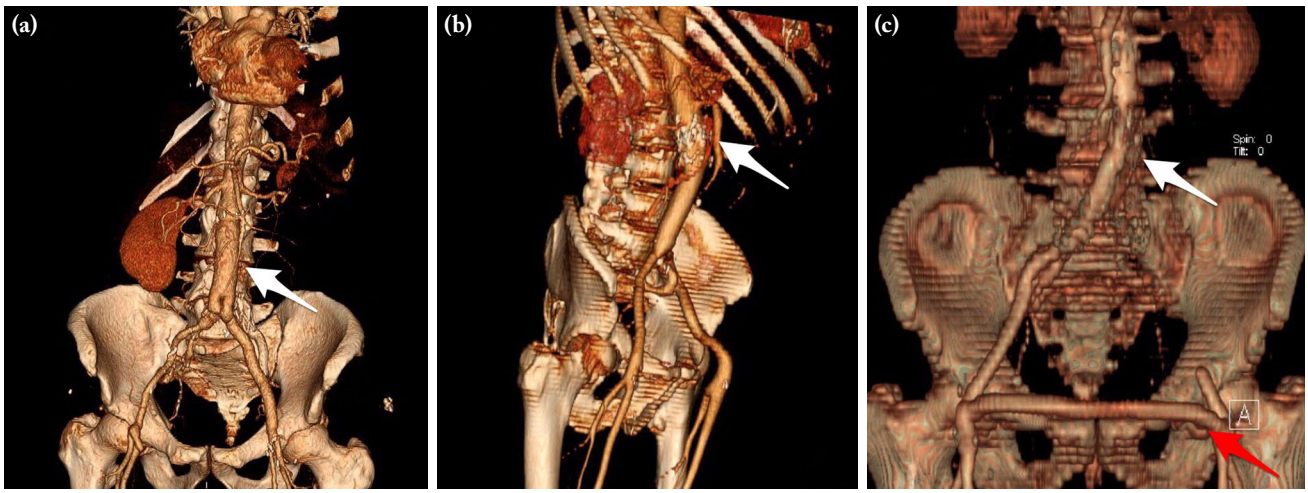

Figure 2. Three-dimensional computed tomographic angiography showed different techniques in surgical conversion after EVAR; **(a)** aortobiiliac bypass graft after total endograft explantation; **(b)** bilateral aortofemoral bypass after partial endograft explantation; **(c)** cross-femoral bypass (red arrow) with total endograft preservation in a patient with left iliac limb occlusion of endograft (white arrow).

EVAR: Endovascular aneurysm repair.

Table 6
Mortality in patients undergoing late SC (n=9)

	30-Day mortality				
	No		Yes		
	n	%	n	%	*p*
Emergency status					
No	5	100	0	0	3.214†
Yes	2	50	2	50	0.167*
Stent graft explantation					
Partial	2	66.7	1	33.3	1.509†
Total	2	66.7	1	33.3	1.000*
Total preservation	3	100	0	0	

SC: Surgical conversion; † Chi-squared test; * Fisher exact test.

Overall, partial stent graft removal was performed in three (33.3%), complete stent graft removal in three (33.3%), and complete preservation of stent graft in three (33.3%) patients. The mean duration of the operation was 214.7±44.8 min, and the mean amount of intraoperative blood loss was 550±235.7 mL.

Overall postoperative complications and outcomes

Overall, perioperative mortality occurred in one hemodynamically unstable patient operated for aneurysm rupture. One of the patients who presented with rupture died due to acute renal failure and pulmonary complications in the ICU after emergency SC. The 30-day overall mortality rate was 22.2%, and all of these patients underwent late SC in the emergency setting. In addition, one patient required temporary renal dialysis and reoperation due to abdominal wound dehiscence, which required prolonged ICU (five days) and hospital stay (30 days). The median length of ICU stay was 2.2 [1-5] days and the median hospital stay was 10 [4-30] days. The 30-day mortality rate in the emergency group (50%) was higher than in the elective group (0%), although it did not reach statistical significance (p=0.167) (Table 6). No late death was recorded during a mean follow-up period of 21±11.9 months.

DISCUSSION

Since the first successful endovascular AAA repair two decades ago, EVAR has been increasingly preferred as a safe procedure. Although the process of aneurysm removal with EVAR is undoubtedly beneficial compared to surgery in terms of operative mortality, length of hospital stay and recovery, the advantage in early outcomes is not reflected in the long-term outcomes.[9] The Endovascular versus Open Repair of Abdominal Aortic Aneurysm (EVAR-1) trial reported that the early advantages were completely lost in long-term, and it was associated with a higher rate of aneurysm-related complications and mortality at four years after EVAR.[10]

Despite the technological advances, the need for late reintervention after EVAR remains constant and may even increase over time.[11] Although most endograft failures after EVAR are corrected endovascularly, late SC is inevitable in some cases. Therefore, long-term surveillance is essential to monitor stent graft-related complications following EVAR. A recent review reported that late open conversion occurred in 0.4 to 22% of patients undergoing EVAR, with an overall rate of 1.9%.[12] In our cohort, the reintervention rate was 9.1% and late SD rate was 1.02%. Furthermore, as previously reported, endovascular reintervention was attempted in four of nine patients who underwent late SC as a salvage procedure.[13]

Late SC may be indicated for multiple reasons, including endoleak with or without sac expansion, stent-graft migration, rupture and thrombosis, or stent-graft infection.[4] In our series, the most frequent reason for late SC was type 3 endoleak with aneurysm sac expansion, followed by graft migration with sac expansion and rupture. Moreover, four patients presented with more than one indication for conversion, consistent with the literature.[14]

A late SC after EVAR is more challenging than standard elective aortic repair due to periaortic inflammation and fusion of the stent graft to the aortic wall.[4] Various surgical strategies for the management of late SC have been reported, particularly three important points: *(i)* surgical approach, *(ii)* aortic cross-clamping site, *(iii)* stent graft removal options.[15]

Transperitoneal or retroperitoneal approaches can be performed with similar efficacy for surgical exposure of the aneurysm sac, and their use depends on experience and preference of the surgeon.[4] In our study, we performed a midline transperitoneal approach in seven of nine patients and an approach without opening the abdominal wall in two patients with stent graft thrombosis. Based on our experience, the midline transperitoneal approach is the main technique in our clinic.

The site of aortic cross-clamping is another important consideration in the operative management of late SC. Performing proximal aortic cross-clamping as far away from the stent graft as possible allows for better exposure and mobilization of the proximal end of the stent graft.[14] In our study, we preferred suprarenal aortic clamping in four patients and thoracic aortic clamping in one patient. The majority of these patients were operated in the emergency setting. However, infrarenal cross-clamping is advantageous in reducing the risk of renal and visceral ischemic injury.[16] Therefore, it is recommended that proximal aortic cross-clamping should be gradually shifted distally as soon as possible.[17] In two patients with stent graft thrombosis, we were able to correct the complication without aortic clamping after EVAR. In these patients, axillobifemoral bypass and cross-femoral bypass grafting were our treatment of choice to minimize the operative risk.

The decision regarding stent graft management during SC (complete/partial stent graft removal or complete preservation) is still a controversial issue, although it usually depends on the indication for reintervention, the intraoperative condition, and the surgeon's preference. Although some authors have advocated that complete removal of the stent graft is the safest surgical intervention to avoid possible late complications,[15] it has been suggested that explantation maneuvers may increase the risk of intraoperative aortic injury, particularly in well-incorporated endografts.[18] In general, we prefer to perform complete removal of the stent graft only, when late SC is indicated due to graft infection and proximal endoleak, as reported by Forbes et al.[19] However, lifelong surveillance is mandatory due to the risk of late complications from the retained portion of the stent graft.[20] No late complications or mortality were observed in our cohort after late SC.

In the current study, we calculated the cut-off value for the initial aneurysm diameter of ≥66 mm for the need for a second EVAR intervention. Since only one of 98 patients underwent late SC,

no statistically significance can be made for this group. These findings may provide a guide for surveillance programs in patients after EVAR, but more research is needed to investigate this hypothesis. Among all patients who underwent late SC, the 30-day mortality rate in the emergency group was higher than elective group, similar to other series.[4] These findings support the aforementioned observation and also demonstrate the importance of the surveillance program.

Nonetheless, there are some limitations to this study. First, the study has a single-center, retrospective design, which limits the representation ability for the whole population. Second, the small number of patients with late conversion after EVAR in our institute prevented us from drawing statistically significant conclusions. Therefore, further multi-center, large-scale, prospective studies are needed to confirm these findings.

In conclusion, despite technological advances, the need for late reintervention after EVAR remains constant and may even increase over time. Late SC, although rarely necessary, remains a challenging issue after failed EVAR. Elective SC seems to be associated with more favorable outcomes. Late SC in elective cases can be safely and successfully performed before serious adverse events occur. The likelihood of need for reintervention after EVAR is higher in patients with an AAA diameter of ≥66 mm. The surveillance program after EVAR is of utmost importance to ensure that patients do not need urgent conversion, particularly in patients with an initial aneurysm diameter of ≥66 mm.

Ethics Committee Approval: The study protocol was approved by the Dr. Siyami Ersek Chest Heart and Vascular Surgery Training and Research Hospital Ethics Committee (date: 20.05.2016, no: 28001928-051.99). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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

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

Author Contributions: Idea, design, data collection, literature review, wrting the article: S.A.; Data collection, literature review, design: S.B.E.; Data collection: M.S.; Control, crtitical review: O.S.; Design, supervision, critical review: E.K.; Supervision, critical review: S.A.A.

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Evaluation of endothelial dysfunction with coronary flow reserve measurement in patients with fibromyalgia

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ABSTRACT

Objectives: This study aims to investigate the role of increased inflammation and oxidative stress over endothelial functions with echocardiographic evaluation of coronary flow reserve in patients with fibromyalgia (FM).

Patients and methods: Between December 2021 and September 2022, a total of 38 female patients (mean age: 43.4±7.0 years; range, 34 to 51 years) with the diagnosis of FM and 35 healthy controls (15 males, 20 females; mean age: 41.1±6.3 years; range, 34 to 49 years) were included. The endothelial functions were evaluated by measuring coronary flow reserve. Coronary flow reserve of the left anterior descending coronary artery was measured from distal and middle portions with pulse wave Doppler at both baseline and hyperemic peak diastolic flow rate by transthoracic echocardiography.

Results: There were no significant differences in clinical, demographical and laboratory findings between the FM and control group, except for conventional C-reactive protein (CRP) levels. The mean hyperemic peak diastolic flow rate and coronary flow reserve values were significantly lower in FM patients ($p<0.001$).

Conclusion: Chronic stress and pain augment the sympathetic activity, resulting in endothelial dysfunction and increasing the cardiovascular risk. Endothelial dysfunction should be evaluated by measuring coronary flow reserve in FM patients.

Keywords: Coronary artery, endothelial dysfunction, fibromyalgia, two-dimensional Doppler echocardiography.

Fibromyalgia (FM) is defined as a chronic syndrome characterized with widespread musculoskeletal pain, fatigue, sleep disturbances, cognitive symptoms, anxiety, and depression.[1] Genetic, neurological, and immunological disorders are known to be the etiological causes of FM.[2] The prevalence of FM is reported to be 5.4% and increases with age, reaching a peak around the seventh decade of life and, at every age, it is more common in women than in men.[3] Risk factors include genetic disorders, female sex, and additional painful conditions. According to the 2010 American College of Rheumatology (ACR) criteria, FM has an approximately 2:1 female-to-male predominance and is reported to be 20 to 30% in patients with systemic lupus erythematosus and rheumatoid arthritis.[4] Symptoms and signs of FM are chronic (>3 months) widespread or multisite pain (≥6 of 9 body regions), fatigue, cognitive problems, sleep disturbances, other somatic symptoms (paresthesia, abdominal pain, headaches, dizziness) and significant soft tissue tenderness on physical examination. The differential diagnosis includes neurological, rheumatological, endocrine and infectious disorders.

Although the pathophysiology of FM has not yet been fully elucidated, endothelial dysfunction and inflammation have been suggested to occur in patients with FM.[5] There is a cerebral blood flow variability in FM patients with a positive correspondence between the emotional and cerebral functional variables which suggests a connection between both cerebral and vascular dysfunction.[6] The increase and overstimulation in sympathetic activity should

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be the main reason for the endothelial damage which can enhance the vascular response.[7] The enhanced vascular response may lead to endothelial dysfunction and damage which probably causes endothelium-mediated atherogenesis.[8] With regard to endothelial nitric oxide (NO) and/or endothelial-derived endothelin 1 (ET-1) releasing defects and decreases in serum NO and/or ET-1 levels, endothelium-related vasodilatation significantly reduces.[9] It has been reported that baroreflex sensitivity reduces in FM patients which accompanies the risk of endothelial dysfunction and enhanced arterial stiffness due to autonomic dysfunction.[10]

Endothelial dysfunction is one of the primary causes of atherosclerosis and, thus, inadequate vasodilatory response and endothelial dysfunction includes increased proinflammatory and prothrombotic states.[11] Endothelial functions can be evaluated with the coronary flow reserve (CFR), which is also known as myocardial flow reserve. It can be measured with both transthoracic and transesophageal echocardiography or invasively with a Doppler-tipped coronary guidewire to determine coronary velocity. A CFR value is defined as the ratio between the hyperemic peak diastolic flow rate (HPDFR) and baseline peak diastolic flow rate (BPDFR) assessed from middle or distal left anterior descending coronary artery (LAD). The normal value for CFR is 2 to 3, whereas ≤2.0 is considered abnormal.[12] Reduced CFR revealing coronary microcirculer dysfunction has been suggested to be the early sign of atherosclerosis.[12] Early stages of the atherosclerotic coronary artery disease is often associated with abnormal resistance of the coronary arteries before obvious stenosis.[13] Diffuse atherosclerotic disease of the epicardial coronary arteries frequently causes impaired CFR which may contribute to myocardial ischemia and perfusion deficiency.

PATIENTS AND METHODS

This single-center, prospective study was conducted at Medicana International Istanbul Hospital Department of Cardiology between December 2021 and September 2022. The study group included 38 female patients (mean age: 43.4±7.0 years; range, 34 to 51 years) who were admitted to either Physical Medicine and Rehabilitation or Rheumatology outpatient clinics of our hospital and diagnosed with FM according to the 2016 revised ACR criteria. The control group was consisted of 35 healthy, asymptomatic, and very low-risk individuals (15 males, 20 females; mean age: 41.1±6.3 years; range, 34 to 49 years) in terms of endothelial dysfunction who were admitted for a regular check-up with no cardiovascular or other systemic diseases. The control group was mainly consisted of those without hyperlipidemia, dyslipidemia and who did not smoke. Exclusion criteria included coronary artery disease, significant valvular heart disease, diabetes mellitus, hypertension, hyperlipidemia, dyslipidemia, psychiatric disease, and thyroid dysfunction. Demographic, clinical, and laboratory data of both groups were recorded.

Routine transthoracic echocardiographic evaluations were performed with VIVID 7 (General Electric, Horten, Norway) by using 3 MHz probe in the left lateral supine position. M-mode echocardiography and 2D measurements were performed according to the American Society of Echocardiography (ASE) guidelines.[14]

All CFR measurements were performed with apical two-chamber long-axis imaging of left ventricle. The middle and distal LAD flow was visualized by color Doppler with an optimal velocity of 12 to 15 cm/sec. Coronary flow of the middle or distal LAD was examined over the epicardial part of the anterior left ventricular wall by color Doppler flow mapping (Figure 1a). The BPDFR was measured initially. All patients had Doppler recordings with a dipyridamole infusion at a rate of 0.56 mg/kg over 4 min. Continuous heart rate and electrocardiographic monitoring was performed simultaneously, as well as blood pressure recordings at baseline, during dipyridamole infusion, and recovery. If the heart rate was increased less than 10% compared to baseline, additional 0.28 mg/kg of dipyridamole infusion over 2 min was administered intravenously. After recovery, the HPDFR was measured. The CFR was calculated by the ratio of the HPDFR-to-BPDFR. A CFR value between 2 and 3 considered normal, whereas <2 values were considered abnormal. The HPDFR measurements using M-mode echocardiography and two-dimensional (2D) Doppler echocardiography of a patient with FM and a healthy control are presented in Figure 1b, c.

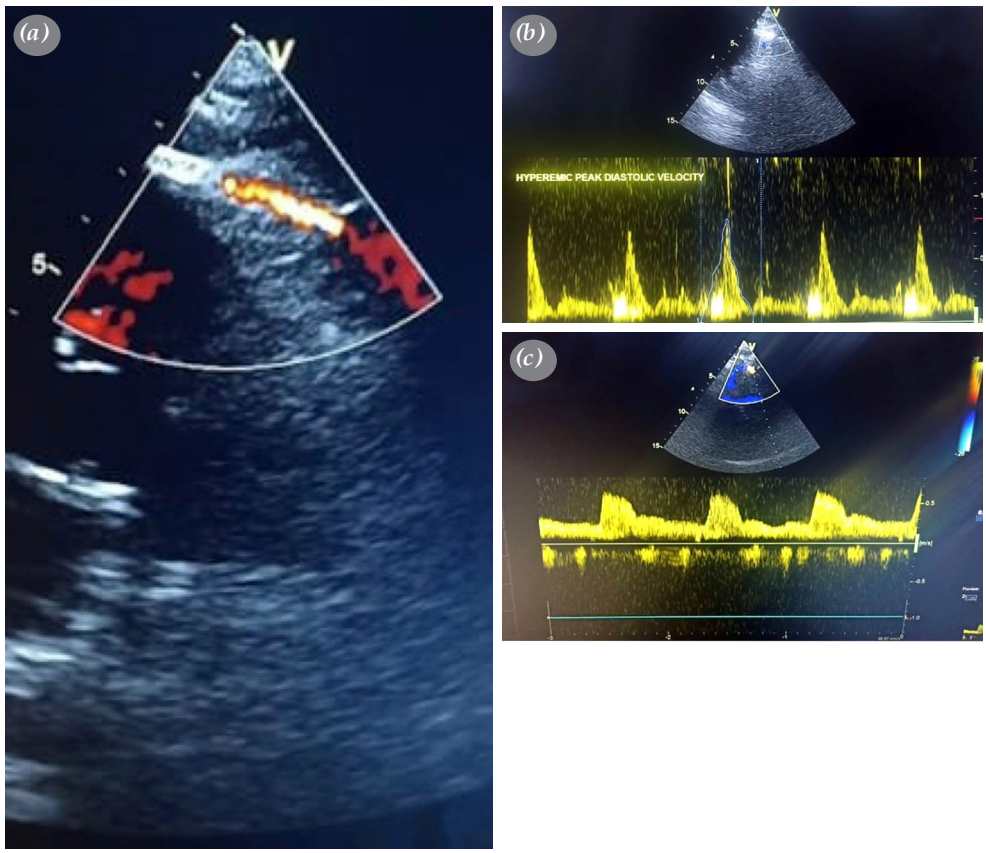

Figure 1. **(a)** Coronary flow reserve measurements were performed with apical two-chamber long-axis imaging of left ventricle. Middle and distal LAD flow was visualized by color Doppler with an optimal velocity of 12 to 15 cm/sec. Coronary flow of middle or distal LAD was examined over the epicardial part of the anterior left ventricular wall by color Doppler flow mapping. **(b)** Transthoracic echocardiographic images of a control group patient. Hyperemic diastolic flow was measured by pulsed-wave Doppler in distal LAD segment. **(c)** Transthoracic echocardiographic images of an FM patient. Hyperemic diastolic flow was measured by pulsed-wave Doppler in distal LAD segment.

LAD: Left anterior descending coronary artery; FM: Fibromyalgia.

Statistical analysis

Statistical analysis was performed using the SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Continuous data were presented in mean ± standard deviation (SD) or median (min-max), while categorical data were presented in number and frequency. The compatibility of quantitative data with a normal distribution was examined using the Shapiro-Wilk test. In terms of quantitative data, the Student t-test or Mann-Whitney U test was used for the comparisons of the groups. In terms of categorical data, the chi-square test was used to compare the groups. In order to predict the HPDFR, CFR and C-reactive protein (CRP) levels, area under curve (AUC), sensitivity and specificity values and 95% confidence intervals (CIs) under the receiver operating characteristics (ROC) curve were used and the diagnostic accuracy of significant variables in the univariate analysis was examined. The most optimal cut-off value was determined, as the value corresponding to the maximum Youden index (J=Sensitivity+Specificity-1). The HPDFR, CFR, and CRP levels were also determined in the univariate regression model with analysis of variance (ANOVA). The "pROC" library was used in the R program (by Xavier Robin, Switzerland) for ROC analysis. A p value of <0.05 was considered statistically significant.

Table 1
Demographic, clinical, and laboratory data of study participants

	FM patients (n=38)				Controls (n=35)				
	n	%	Mean±SD	IQR	n	%	Mean±SD	IQR	*p*
Age (year)			43.4±7.0	34-51			41.1±6.3	34-49	0.14‡
Sex									0.26*
Male					15	43			
Female	38	100			20	57			
BMI (kg/m²)			25.3±4.4	23.2-31.4			25.5±2.3	23.3-31.2	0.81‡
SBP (mmHg)			118.6±10.2	102-128			116.6±9.6	106-127	0.99‡
DBP (mmHg)			75.4±5.8	70-84			76.4±6.3	69-83	0.76‡
Heart rate (bpm)			73.7±3.5	66-82			73.4±10.6	61-85	0.85‡
FBS (mg/dL)			102.67±47.57	89-115			98.07±31.17	84-112	0.75‡
Total cholesterol (mg/dL)			183.5±28.8	152-198			181.6±31.1	140-186	0.74‡
HDL (mg/dL)			49.73±13.21	36-65			48.53±14.78	35-64	0.88‡
LDL (mg/dL)			115.67±26.16	100-130			107.76±20.80	92-125	0.45‡
Triglyceride (mg/dL)			130.4±27.26	104-198			147.2±33.49	98-182	0.33‡
Fibrinogen (mg/dL)			410.8±133.27	320-480			388.93±117.62	298-466	0.20‡
CRP (mg/mL)			2.29±1.39	0.6-3.8			1.49±1.04	0.5-2.9	**0.019**‡
HOMA-IR			2.45±1.93	1.8-2.9			2.42±1.21	1.7-2.6	0.72‡
Hemoglobin			12.5±1.3	10.6-13.0			13.3±0.90	10.8-13.2	0.12‡

FM: Fibromyalgia; SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-reactive protein; HOMA-IR: Homeostasis model assessment-insulin resistance. P value extracted from † Student's t-test; ‡ Mann-Whitney U test (U); * Chi-square test.

RESULTS

Demographic, clinical, and laboratory data of the patients and healthy controls are summarized in Table 1. There were no significant differences in demographic, clinical, and laboratory findings between the FM and control group, except for the mean conventional CRP levels which were 2.29±1.39 (range, 0.6 to 3.8) mg/mL in the patient group and 1.49±1.04 (range, 0.5 to 2.9) mg/mL in the control group, respectively (p=0.019).

The mean global left ventricular ejection fraction (LVEF), end-diastolic (ED) septum and posterior

Table 2
Transthoracic echocardiographic parameters of the FM and control group patients

	FM patients (n=38)		Controls (n=35)		
	Mean±SD	IQR	Mean±SD	IQR	*p*
Septum-ED (cm)	0.94±0.13	1.1-0.7	0.94±0.14	1.1-0.8	0.74†
PW-ED (cm)	0.92±0.08	1.08-0.74	0.91±0.07	1.07-0.72	0.71†
LVEF (%)	66±4.59	58-67	65.5±2.57	59-69	0.67†
BPDFR (cm/sec)	31.6±8.3	25.6-39.1	33.45±7.37	27.8-41.6	0.912†
HPDFR (cm/sec)	64.8±9.12	53.5-72.9	78.15±14.32	66.7-91.3	<0.001†
CFR (cm/sec)	2.05±0.19	1.63-2.41	2.39±0.23	2.02-2.73	<0.001†

FM: Fibromyalgia; IQR: Interquartile range; ED: End-diastolic; PW: Posterior wall; LVEF: Left ventricular ejection fraction; BPDFR: Baseline peak diastolic flow rate; HPDFR: Hyperemic peak diastolic flow rate; CFR: Coronary flow reserve. P value extracted from † Mann-Whitney U test.

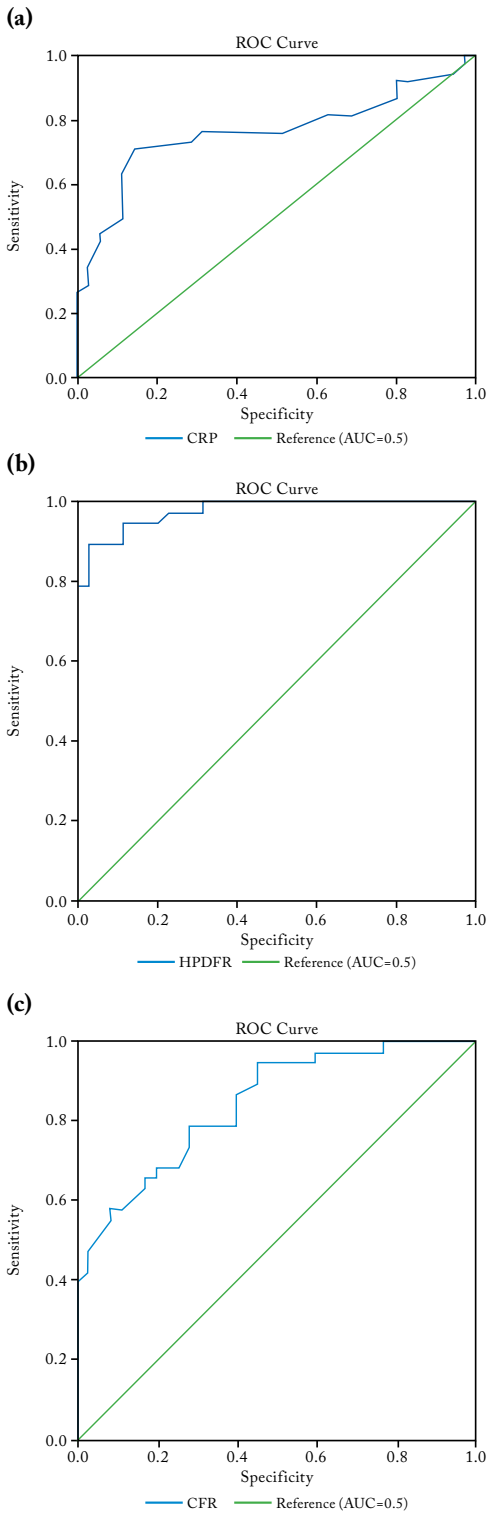

Figure 2. **(a)** Diagnostic accuracy of CRP values - ROC curve. **(b)** Diagnostic accuracy of HPDFR values - ROC curve. **(c)** Diagnostic accuracy of CFR values - ROC curve.

ROC: Receiver operating characteristics; HPDFR: Hyperemic peak diastolic flow rate; AUC: Area under curve; CRP: C-reactive protein; HPDFR: Hyperemic peak diastolic flow rate; CFR: Coronary flow reserve.

wall (PW) thicknesses, and BPDFR measurements were all within normal ranges for both the patient and control groups. However, the mean HPDFR and CFR values were significantly lower in FM patients ($p<0.001$). The transthoracic echocardiographic parameters of all participants are given in Table 2.

Diagnostic accuracy of CRP, HPDFR, and CFR values with the ROC diagrams and the ANOVA analysis are depicted in detail in Figure 2. Accordingly, conventional CRP levels, HPDFR and CFR values of the fibromyalgia patients were quantifying a diagnostic accuracy within the endothelial dysfunction.

DISCUSSION

The main objective of our study was to investigate the role of increased inflammation and oxidative stress over endothelial functions with transthoracic echocardiographic evaluation of the CFR and HPDFR in patients with FM. The primary endpoint of the study was to evaluate endothelial dysfunction which should be determined by CFR and HPDFR measurements to prove FM as a cardiovascular risk factor. The CFR is a combined measurement of the vasodilator capacity of coronary microcirculation, which is an independent predictor of long-term prognosis of atherosclerosis.[15] We evaluated endothelial dysfunction which was revealed by decreased levels of CFR and HPDFR in patients with FM. Our study results showed that HPDFR and CFR values were significantly reduced in FM patients. In addition, conventional CRP values were also higher in these patients. Similarly, Bote et al.[16] confirmed that FM patients had an inflammatory state accompanied by an altered stress response. This is mainly manifested by high circulating levels of interleukin (IL)-8 and CRP (in 100% of the FM group). There is also an increased release of inflammatory cytokines (IL-1β, tumor necrosis factor-alpha, IL-6, IL-10, IL-18 and monocyte chemoattractant protein-1) by monocytes, and enhanced activation of the functional capacity of neutrophils (chemotactic, phagocytic and fungicidal activities).[16] The etiopathogenesis of FM is multifactorial. Apart from neurohormonal and genetic factors, increased inflammatory activity and oxidative stress are known to play a role in the development of FM.[16,17] Thus, data on CRP are also controversial. A large-scale study showed a positive association between CRP and FM.[18] However, this association was attenuated after adding body mass index and

comorbidities in the model. The fact that these conditions, which are included in the pathophysiology of endothelial dysfunction and atherosclerosis, suggests that the endothelial functions of patients with FM may also be impaired and, thus, FM and endothelial dysfunction may accompany. Endothelial cells and endothelium-derived cytokines are other modulators of inflammation. A study by Mertoglu et al.[5] revealed that the level of endocan, a proteoglycan produced by endothelial cells, was significantly higher in patients with FM, compared to healthy controls. Increased levels of cytokines induced by inflammatory reaction and catecholamine-induced endothelial damage including microvascular spasm may be related with the pathophysiological mechanisms of decreased CFR in FM patients.[8] Vascular endothelial cells modulate the vascular tone either by secreting relaxing or constructing mediators. The ET1 is one of the potent vasoconstrictor peptides which is oversecreted by the endothelium and the vascular smooth cells as a result of inflammatory conditions. These levels increase in patients with FM.[8]

Coronary microvascular spasm plays a major role in affecting myocardial ischemia in patients without obstructive coronary artery disease and also associated with female predominance.[19] Similarly, Suwaidi et al.[20] reported that coronary endothelial dysfunction without obstructive coronary lesions was significantly associated with advanced cardiovascular disease. Likewise, endothelial and microvascular dysfunction, abnormal neurohormonal activity, and small vessel disorders may lead to coronary slow flow which ranges from 1 to 6% among patients with suspected coronary artery disease.[21] The coronary circulation may be sensitized to the circulating vasoconstrictor catecholamines by microvascular endothelial dysfunction in terms of inflammatory processes. Nevertheless, chronic pain may impair coronary circulation as a result of immoderate triggering of sympathetic nervous system (SNS) in FM patients.[22] Increased sympathetic activity can change cardiovascular responses and cause endothelial dysfunction. Nitric oxide, which is produced by catalyzing L-arginine, has a critical function in vasodilatation. Activated SNS decreases endothelial-derived vasodilatation caused by a loss of NO bioavailability in the vessel wall, although this process limits the relaxation ability of the artery and impairs the smooth cell functions.[23] The link between the immune and nervous systems is implicated in the pathophysiology of FM-related vascular disorders.

Flow-mediated vasodilation (FMD) test is the most accepted non-invasive test which reflects arterial endothelial-mediated vasomotor function.[24] Due to possible side effects of the administered drugs or invasive patterns of procedures to evaluate the endothelial functions, endothelial function measurement through FMD shows high accuracy.[25]

Cardiovascular diseases are considered major causes of morbidity and mortality.[26] Patients with FM can be also evaluated regarding the cardiovascular risk factors. Reducing the pain and diminishing the severity of disease can be crucial to prevent cardiovascular risk factors in patients with FM. Our findings suggest that CFR is a possible predictor of long-term prognosis of atherosclerosis in FM patients which would call attention to the long-term impacts of living with FM. Further studies are, therefore, required to confirm FM as a cardiovascular risk factor.

The fact that the entire population in the patient group was female is the main limitation to this study. During the study period, no male patients were admitted to either Physical Medicine and Rehabilitation or Rheumatology outpatient clinics of our center with the diagnosis of FM. Additionally, the menstrual cycle of the patients were not considered and different hormonal phases may have affected cardiovascular variables. Finally, the findings of our study are only preliminary data and further large-scale, prospective studies are needed for future considerations about coronary flow dynamics in FM patients.

In conclusion, chronic stress and pain augment the sympathetic activity, resulting in endothelial dysfunction and increasing the cardiovascular risk. Endothelial dysfunction should be evaluated by measuring coronary flow reserve in FM patients.

Ethics Committee Approval: This was a prospective and single-center study which was approved by the Medicana International Istanbul Hospital Ethics Committee (date: 03.11.2021, no: 022) and was conducted by the principles of the Helsinki Declaration. Ethical consent had also been obtained for intravenous drug administration during the CFR measurements.

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

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

Author Contributions: Idea/concept, data collection and/or processing, design: G.G.; Design, analysis and/or interpretation: E.B.K.; Literature review, writing the article, critical review: B.Ş.

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Predictors of contrast nephropathy after percutaneous intervention of chronic total occlusion in patients with chronic coronary syndrome: A single-center study

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ABSTRACT

Objectives: This study was planned to determine the predictors of contrast nephropathy developing after percutaneous coronary intervention (PCI) in patients who underwent coronary angiography due to chronic coronary syndrome and were found to have chronic total occlusion (CTO).

Patients and methods: The retrospective observational study included 110 patients with chronic coronary syndrome who were diagnosed with CTO between March 2017 and February 2023. All patients were divided into two groups: 53 patients (29 males, 14 females; mean age: 62.8±10.2 years; range, 42 to 84 years) who developed contrast-induced nephropathy (Group 1) and 57 patients (38 males, 19 females; mean age: 58.8±11.2 years; range, 37 to 79 years) who did not (Group 2).

Results: The mean age of the patients in Group 1 was statistically greater than in Group 2 (p=0.04). In the multivariate regression analysis we performed for the prediction of contrast nephropathy in patients with CTO, chronic renal failure (OR: 0.025; 95% CI: 0.001-0.430, p=0.01), amount of opaque substance (OR: 1.115; 95% CI: 1.031-1.206, p=0.006), left ventricular ejection fraction (OR: 0.683; 95% CI: 0.551-0.847, p=0.001), and glucose (OR: 1.046; 95% CI: 1.014-1.078, p=0.004) were found to be independent predictors of contrast nephropathy.

Conclusion: Our study revealed that baseline high creatinine (underlying chronic renal failure), high blood sugar that increases plasma osmolarity (uncontrolled diabetes mellitus), high amount of opaque material used, and low left ventricular ejection fraction are predictors of post-PCI contrast nephropathy. Paying attention to correctable risk factors before giving opaque material to patients for whom PCI is planned is valuable in terms of reducing kidney damage.

Keywords: Chronic coronary syndrome, chronic total occlusion, contrast nephropathy, predictor.

Atherosclerosis shows a progressive course as a result of inflammation, which causes coronary artery disease and shows systemic involvement.[1] In the 2019 European Society of Cardiology chronic coronary syndrome (CCS) guideline, patients with stable coronary artery disease were defined as CCS, and new protocols were developed for these patients. Coronary angiography (CAG) and percutaneous coronary intervention (PCI) are still the primary options in the diagnosis and treatment of these patients.[1]

Chronic total occlusion (CTO) is a condition that is characterized by complete occlusion of the coronary arteries for at least three months and is encountered in approximately 20% of CAGs (Figure 1). Apart from being detected as a vascular occlusion not associated with infarction in patients with acute coronary syndrome, it can also be seen in patients with CCS. Chronic total occlusion is attempted to be treated with PCI or coronary artery bypass graft, but the results can sometimes be unfavorable.[2-4] The method chosen for treatment is affected by various factors. Factors such as the experience of the operator, selected PCI materials (such as guide catheter, guide wire), location, length, anatomy of coronary occlusion, and presence of calcification are important.[5] Revascularization of CTO takes more time and may cause various complications since it is an area of interventional cardiology with a high level of difficulty.

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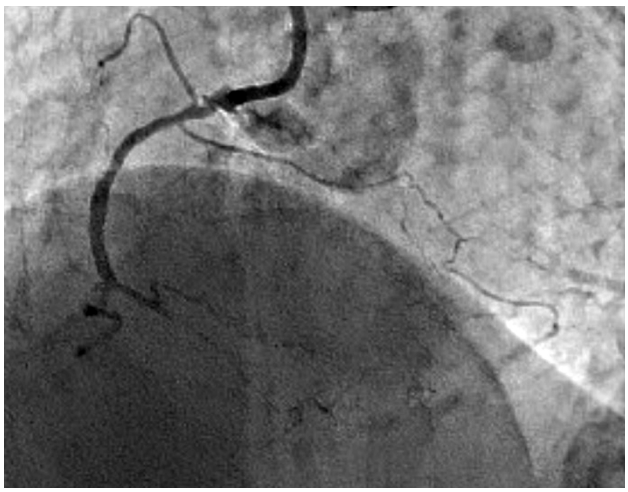

Figure 1. Coronary angiography image of a patient with chronic total occlusion.

Although the most important instrument used during PCI is the contrast agent (opaque material), one of the undesirable effects is contrast agent-induced nephropathy. It has been suggested that contrast media-induced nephropathy occurs with the synergistic effect of direct renal tubular cell toxicity and renal medullary ischemia. Contrast nephropathy is thought to occur with direct cytotoxicity, cell damage after contrast administration, and histological changes in enzymuria.

The nature of the contrast, associated ions, concentration, and concomitant hypoxia are important for the degree of cellular damage, while the osmolality of the solution appears to be of secondary importance. Contrast injection causes a biphasic hemodynamic change in the kidney, with an initial transient increase followed by a longer-lasting reduction in renal blood flow.[6,7] In previous studies, the reasons that increase contrast nephropathy were examined and clinical conditions to be avoided were explained. The most important thing is the presence of chronic renal failure (CRF), a history of diabetes mellitus (DM), and heart failure.[8] This study aimed to determine the predictors of contrast nephropathy in patients with CCS who underwent PCI for CTO.

PATIENTS AND METHODS

The retrospective observational study included 110 patients with CTO who applied to the cardiology outpatient clinic of the Bakırçay University Çiğli Training and Research Hospital between March 2017 and February 2023 and were diagnosed with CCS with noninvasive tests and underwent CAG. Patients older than 18 years of age and with optimal CAG images were included in the study. Patients with a history of percutaneous transluminal coronary angioplasty with coronary artery bypass graft, those with active infection or severe liver failure, and patients whose kidney function test results could not be obtained were excluded from the study. Demographic data, comorbid histories, routine blood tests and transthoracic echocardiography data of the patients in the study were noted by looking at the hospital data recording system. All patients were divided into two groups: 53 patients (29 males, 14 females; mean age: 62.8±10.2 years; range, 42 to 84 years) who developed contrast-induced nephropathy (Group 1) and 57 patients (38 males, 19 females; mean age: 58.8±11.2 years; range, 37 to 79 years) who did not (Group 2).

Smoking was accepted if the patients were active users according to their verbal expressions. Blood pressure above 140/90 mmHg with repeated measurements or the use of oral antihypertensive drugs was defined as having hypertension, which is one of the comorbidities. A glomerular filtration rate below 60 mL/min for CRF, total cholesterol >200 mg/dL, low-density lipoprotein cholesterol >130 mg/dL or triglyceride >150 mg/dL for hyperlipidemia, and for heart failure left ventricular ejection fraction (LVEF) <50% was taken as the defining criterion. A 25 to 50% increase in serum creatinine levels at 48 h post angiography from baseline is recommended to define contrast nephropathy.[9,10]

Coronary angiography was performed on all patients in the study using the standard Judkins technique. The patients were started with the necessary premedication during PCI. Dual antiplatelet therapy was given at a loading dose for each patient. Coronary angiography images were viewed via the imaging software system, and the presence of CTO in any coronary artery, the presence of calcification in the relevant coronary artery, and the development of collateral circulation were evaluated. The data of the opaque substance used during PCI and the duration of the interventional procedure for these patients, which can be accessed through the hospital information management system, were noted.

Statistical analysis

Data were analyzed using IBM SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Distribution normality analysis of continuous variables was evaluated according to the Shapiro-Wilk test. Normally distributed continuous variables were analyzed with Student's t-test and presented as mean and standard deviation. Nonnormally distributed continuous variables nonnormally distributed were presented as median and interquartile range and analyzed using the Mann-Whitney U test. Categorical variables were reported as number and frequency and assessed using the Pearson chi-square test and Fisher exact test. Logistic regression analysis was performed to estimate the presence of contrast nephropathy. A p-value <0.05 was considered statistically significant.

RESULTS

The mean age of the patients in Group 1 was statistically greater than in Group 2 (62.8±10.2 years *vs.* 58.8±11.2 years, p=0.04). Among the comorbid

Table 1
Demographic, clinical, and angiographic characteristics

	Contrast nephropathy (+) (n=53)			Contrast nephropathy (–) (n=57)			
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			62.8±10.2			58.8±11.2	0.04
Sex							
Male	29	55		45	67		0.16
Smoking	21	40		27	40		0.94
Hypertension	24	45		21	31		0.11
Diabetes mellitus	24	45		18	27		0.03
Heart failure	29	55		15	22		0.001
Chronic renal failure	11	20		5	7		0.03
Hyperlipidemia	12	23		16	24		0.87
Drugs							
Oral antidiabetics	22	41		16	24		0.04
Insulin	3	6		4	6		0.63
Betablocker	10	19		5	7		0.06
Calcium channel blocker	7	13		8	12		0.83
RAS blocker	23	43		21	31		0.17
Statin	12	23		16	24		0.87
Diuretic	12	23		7	10		0.06
Angiographic findings							
Interference artery							0.09
Right coronary artery	17	32		31	46		
Circumflex artery	13	24		32	48		
LAD artery	23	43		4	6		
Presence of calcification	13	24		7	10		0.05
Duration of PCI (min)			81±20			65±18	**0.001**
Opaque amount (mL)			242±33			200±22	**0.001**
Collateral development	28	52		32	48		0.58

SD: Standard deviation; RAS: Renin angiotensin system; LAD: Left anterior descending; PCI: Percutaneous coronary intervention.

diseases, DM (45% *vs.* 27%, p=0.03) and CRF (20% *vs.* 7%, p=0.03) were significantly higher in Group 1 than in Group 2. Among the angiographic findings of the patients, the duration of coronary intervention (81±20 min *vs.* 65±18 min, p=0.001) and the amount of opaque material used (242±33 mL *vs.* 200±22 mL, p=0.001) were higher in Group 1 than in Group 2. Demographic, clinical, and angiographic characteristics of the patients are shown in detail in Table 1.

Looking at the laboratory analysis results, fasting blood glucose [177 (108-254) mg/dL *vs.* 109 (92-127) mg/dL, p=0.001] and 48th h creatinine [1.23 (1.15-1.36) mg/dL *vs.* 0.93 (0.83-1.05) mg/dL, p<0.001] values were higher in Group 1 than in Group 2. Only two patients who developed contrast nephropathy during follow-up after PCI required acute hemodialysis. Left ventricular ejection fraction measured by echocardiography was significantly lower in Group 1 than in Group 2 [40% (34-50%) *vs.* 50% (50-55%), p<0.001]. Laboratory analysis results of the patients are given in Table 2.

In the univariate regression analysis performed for the prediction of contrast nephropathy in patients with CTO, age [odds ratio (OR): 1.035; 95% confidence interval (CI): 1.000-1.071, p=0.051], DM (OR: 0.444; 95% CI: 0.207-0.953, p=0.04), CRF (OR: 0.308; 95% CI: 0.100-0.951, p=0.04), oral antidiabetic use (OR: 2.262; 95% CI: 1.033-4.952, p=0.04), duration of PCI (OR: 1.045; 95% CI: 1.023-1.068, p<0.001), amount of opaque substance (OR: 1.058; 95% CI: 1.036-1.080, p<0.001), LVEF (OR: 0.852; 95% CI: 0.799-0.909, p<0.001), and glucose (OR: 1.024; 95% CI: 1.013-1.035, p<0.001) were defined as markers of contrast nephropathy. In multivariate regression analysis, CRF (OR: 0.025; 95% CI: 0.001-0.430, p=0.01), amount of opaque substance (OR: 1.115; 95% CI: 1.031-1.206, p=0.006), LVEF (OR: 0.683; 95% CI: 0.551-0.847, p=0.001), and glucose (OR: 1.046; 95% CI: 1.014-1.078, p=0.004) were found to be independent predictors of contrast nephropathy (Table 3).

Table 2
Laboratory results of patients

	Contrast nephropathy (+) (n=53)			Contrast nephropathy (–) (n=57)			
Variables	Mean±SD	Median	IQR (Q1-Q3)	Mean±SD	Median	IQR (Q1-Q3)	*p*
LVEF (%)		40	34-50		50	50-55	**<0.001**
Glucose (mg/dL)		177	108-254		109	92-127	**0.001**
Urea (mg/dL)		37	31-42		34	27-42	0.33
Creatinine (mg/dL)		0.85	0.77-1.04		0.85	0.77-0.97	0.52
Creatinine 48th h (mg/dL)		1.23	1.15-1.36		0.93	0.83-1.05	**<0.001**
Sodium (mEq/L)		139	135-140		138	137-140	0.62
Potassium (mEq/L)		4.3	4.1-4.6		4.4	4.1-4.6	0.63
Calcium (mg/dL)		9.2	8.8-9.5		9.2	8.9-9.5	0.92
Total cholesterol (mg/dL)		152	130-205		168	135-210	0.24
Trygliceride (mg/dL)		139	96-211		146	107-240	0.40
HDL (mg/dL)		43	38-48		43	35-48	0.35
LDL (mg/dL)		73	57-111		86	669-132	0.06
Hemoglobin (mg/dL)		14	12.6-14.8		14.4	12.7-15.2	0.09
Thrombocyte (10^9/L)	243±79			244±66			0.93
White blood cell (10^9/L)	9.12±2.72			9.12±2.46			0.98
Neutrophil (10^9/L)	6.05±2.49			5.71±2.34			0.44

SD: Standard deviation; IQR: Interquartile range; Q: Quartile; LVEF: Left ventricle ejection fraction; HDL: High density lipoprotein; LDL: Low density lipoprotein.

Table 3
Logistic regression analysis

	Univariate logistic regression			Multivariate logistic regression		
Variables	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.035	1.000-1.071	0.051	-		
Diabetes mellitus	0.444	0.207-0.953	0.04	0.580	0.001-303.622	0.86
Chronic renal failure	0.308	0.100-0.951	0.04	0.025	0.001-0.430	0.01
Oral antidiabetic use	2.262	1.033-4.952	0.04	6.635	0.011-4001.272	0.56
Duration of PCI	1.045	1.023-1.068	<0.001	1.013	0.938-1.094	0.74
Opaque amount	1.058	1.036-1.080	<0.001	1.115	1.031-1.206	0.006
LVEF	0.852	0.799-0.909	<0.001	0.683	0.551-0.847	0.001
Glucose	1.024	1.013-1.035	<0.001	1.046	1.014-1.078	0.004

OR: Odds ratio; CI: Confidence interval; PCI: Percutaneous coronary intervention; LVEF: Left ventricle ejection fraction.

DISCUSSION

The main finding of our study is that a history of CRF, excess contrast material used, low LVEF, and high plasma glucose level are predictive of contrast nephropathy in patients with CCS who underwent PCI for CTO. It has been shown in previous studies that the most important predisposing factor in the development of contrast nephropathy is the presence of underlying CRF. Persistence of damage to kidney function after contrast nephropathy has been associated with the degree of CRF. Even if hemodialysis is not needed most of the time, contrast can cause permanent damage in 30% of patients affected by nephropathy.[8-11] In a retrospective study by Lewy et al.,[12] mortality and length of hospital stay were found to be significantly higher when the group that developed contrast nephropathy was compared to the control group, and this result was found due to the findings of acute kidney failure. Again, in the long-term follow-up results of Guzel et al.[13] in patients with CTO, mortality was higher in the group with contrast nephropathy after PCI. The most important measure to avoid contrast nephropathy is to use the least amount of contrast material possible. In previous meta-analyses, the increase in the amount of contrast material used and the use of opaque materials with high osmolarity increased the risk of nephrotoxicity.[14,15]

In previous studies, intravenous fluid administration at least 2 h before and after the procedure to patients with subclinical dehydration before contrast administration has been shown to reduce contrast nephropathy.[16,17] Based on this data, we can conclude that the higher blood osmolarity of patients with higher fasting plasma glucose may lead to contrast nephropathy. In addition, hyperglycemia itself can increase oxidative stress as a result of free oxygen radicals, resulting in both adverse effects on the pathophysiology of DM and damage to the renal tubular system.[18]

Shacham et al.[19] investigated the effect of left ventricular systolic function on acute kidney injury in patients with acute myocardial infarction (AMI) and showed that the prognosis is poor in older patients with impaired renal function and low LVEF. Wang et al.[20] found a higher risk of developing contrast nephropathy in patients with low ejection fraction in their study of the relationship between contrast nephropathy and LVEF after CAG in patients with heart failure. In our study, LVEF was found to be lower in the group with contrast nephropathy.

The main limitations of the study were that it was a single-center study and retrospective in design. In addition, data on hemodynamic variability during the angiography procedure, whether patients were hydrated with intravenous fluid before the procedure, and long-term follow-up results were lacking.

In conclusion, a high creatinine value at baseline (underlying CRF), high blood sugar that increases plasma osmolarity (uncontrolled DM), high amount of contrast agent used, and low LVEF are predictors of contrast nephropathy in patients with CCS who underwent PCI for CTO. Paying attention to the risk factors that can be corrected before the administration

of contrast material to patients is valuable to reduce renal damage.

Ethics Committee Approval: The study protocol was approved by the Bakırçay University Non-Invasive Clinical Ethics Committee (date: 08.03.2023, no: 2023/905). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: Written informed consent was not obtained as this study was retrospective.

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

Author Contributions: Collected study data, wrote the main manuscript, and prepared the tables: F.S.Y.; Performed statistical analyses the article: A.A.B.; Reviewed the article: Y.D., E.O.B.; All authors have read and approved the final article.

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Inhibitory effect of cilostazol on intimal hyperplasia and smooth muscle cell proliferation in a rabbit carotid artery anastomosis model

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ABSTRACT

Objectives: This study aims to investigate the effect of cilostazol on intimal hyperplasia and smooth muscle cell proliferation in a rabbit carotid artery anastomosis model.

Materials and methods: A total of 16 New Zealand male rabbits weighing 2 to 3 kg were used in this study. The rabbits were divided into two groups with eight in each group as Group A and Group B. A vertical neck incision was made in an appropriate position for all group rabbits and the right carotid artery was dissected. The same artery was transected and anastomosis using 8/0 polypropylene was performed with a continuous anastomosis technique. Group A was assigned as the control group and no medication was given. Cilostazol was administrated to Group B at a dose of 25 mg/kg twice a day per oral for 21 days. At the end of Day 21, the anastomosis segments of the right carotid artery and contralateral carotid artery of all rabbits were sent to the histology laboratory for analysis. The lumen diameter, lumen area, intimal area, medial area, and intima/media area ratio were estimated.

Results: In the serial sections, the mean lumen diameter of Group B was found to be significantly higher than Group A (p=0.001). The lumen area of Group B was significantly higher than Group A (p=0.001). The section series were evaluated and the area of the intima of Group B was significantly lower than Group A (p=0.001). The medial area of Group B was significantly larger than Group A (p=0.001). The intima/media area ratio was significantly higher in Group A (p=0.001).

Conclusion: Cilostazol may be useful for preventing intimal hyperplasia and smooth muscle cell proliferation after vascular surgery.

Keywords: Anastomosis, cilostazol, intimal hyperplasia, rabbit, smooth muscle cell proliferation.

Intimal hyperplasia and smooth muscle cell proliferation play an important role in restenosis after vascular interventions. Reconstruction is one of the most common interventions in the management of obstructing artery diseases. Recently, the success of this type of intervention are under expectations due to spontaneous thrombosis or restenosis.[1] After vascular reconstructive interventions, unlikely acute obstruction in which acute thrombosis is important at the late stage, intimal hyperplasia caused by smooth muscle cell migration, proliferation, and extracellular matrix (ECM) deposition are implicated in the pathophysiology of narrowing or restenosis.[2] Intimal hyperplasia is a vasoactive process characterized by vascular smooth muscle cell (VSMC) proliferation, inflammatory cell infiltration, endothelial cell injury, and increased position of the ECM. It begins with endothelial injury and ends up with partial or total restenosis in the long term. These mechanisms produce vascular lumen re-narrowing or restenosis, leading to unsuccessful vascular interventions.[3]

Cilostazol is a selective inhibitor of phosphodiesterase type 3 that increases intracellular cyclic adenosine monophosphate (cAMP) levels and activates protein kinase A, thereby inhibiting VSMC proliferation. It also significantly decrease platelet-derived growth factor (PDGF) in an experimental animal model.[4]

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Cilostazol is manufactured by Otsuka Pharmaceutical Co. Ltd. (Tokyo, Japan) under the trade name Pletal®. Cilostazol is approved for use in the United Kingdom by the National Institute for Clinical Excellence (NICE) and is licensed in the United States since 1999, by the Food and Drug Administration (FDA). It is used to treat patients suffering from intermittent claudication without rest pain and no peripheral tissue necrosis, as it improves pain-free walking distances.[5-9]

In this experimental study, we aimed to investigate the effects of cilostazol on smooth muscle cell proliferation and the formation of neointimal hyperplasia in surgical procedures in a rabbit carotid artery anastomosis model.

MATERIALS AND METHODS

In this experimental, randomized-controlled study, 16 randomly selected New Zealand-type male rabbits weighing 2 to 3 kg on average were included. During the study, all experimental animals were kept under the same conditions (in a room at a temperature of 20±2˚C with a ventilation system and receiving sunlight) and fed with rabbit feed. The rabbits were, then, divided into two equal groups. Group A (n=8) underwent right carotid artery anastomosis and received no medication, while Group B (n=8) underwent right carotid artery anastomosis and received cilostazol for 21 days following surgery. Cilostazol was administered at a dose of 25 mg/kg twice a day per oral immediately after surgery.

Surgical procedure

Before surgery, a cannula was inserted into the marginal ear vein for intravenous access. In both groups, the surgical protocol was the same: for anesthesia, 50 mg/kg of ketamine (intramuscular) and 5 mg/kg of xylazine (intramuscular) were administered. Also, we administered intravenous cefazolin (50 mg/kg) preoperatively to prevent infections. After shaving for better vision during surgery and disinfection with povidone-iodine, a right vertical neck incision was made. The right carotid artery was explored near the trachea. Proximal and distal parts of the right carotid artery were clamped with bulldog clamps after giving 100 IU/kg of heparin by ear vein, and the carotid artery was transected full layer. The artery was anastomosed in an end-to-end fashion with running monofilament sutures (8.0 polypropylene, 6.5 mm 3/8 circle [Ethicon Inc., NJ, USA]). Then, the clamps were removed to re-establish blood flow. Layers were closed in the anatomic plane, and the operation was complete. All procedures were performed with sterile instruments and surgical asepsis by a single operator using an operating microscope. All experimental animals survived the procedure and were followed up for 21 days without any complications. While study animals (Group B) received cilostazol daily per oral, control subjects received normal food and water. At the end of Day 21, all animals were anesthetized using the same protocol. The right anastomosed and the left non-anastomosed carotid artery segments were removed and sent to the histology laboratory for examination. The arterial segments were kept in a 10% buffered formaldehyde solution and sent to the histology laboratory for analysis. All rabbits were sacrificed using 150 mg/kg pentothal at the end of the procedure.

Histological examination

After fixation of the vessels in the 10% buffered formaldehyde solution, they were embedded in paraffin. Serial cross-sections in 5-µm thickness were obtained by cutting the paraffin blocks at the level of the anastomosis with a rotary microtome (Leica RM, 2135; Leica Biosystems Nussloch GmbH, Nußloch, Germany). The arterial specimens were stained using hematoxylin-eosin and Masson's trichrome. The sections of anastomosed and the corresponding contralateral sides were evaluated under a light microscope (Olympus BH-2, Tokyo, Japan). Photomicrographs were taken with a high-resolution JVC TK-890E, video camera (JVC Kenwood Corporation, Yokohama, Kanagawa, Japan). Obtained images were assessed with a digital imaging analysis program (UTHSCSA; Image tool version 3.0 University of Texas, TX, USA). The images were analyzed via a digital image analysis program and lumen diameter, lumen area, intimal area, medial area, and intima/media area ratio were estimated. Serial cross-sections taken from paraffin tissues were captured and transferred to a computer environment. Intimal and medial areas were measured, and the sections were three-dimensioned via Reconstruct version 1.0.9.9 software (JC Fiala; developed by J.C. Fiala and K.M. Harris at Boston University, MA, USA).

Statistical analysis

Statistical analysis was performed using the SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were presented in mean ± standard deviation (SD) or number and frequency, where applicable. The Mann-Whitney U test was used for the comparison between the two groups and the Kruskal-Wallis analysis of variance (ANOVA) test was used for the comparison of the differences between the groups. A p value of <0.05 was considered statistically significant.

RESULTS

Histopathological evaluation

All the animals survived throughout the study, and none of them exhibited neurological deficits or wound infection. Arterial anastomosis was patent in all animals in both groups at the end of the study.

In the histological sections of Group A, the right carotid artery was compared with the left carotid artery. The right carotid artery lumen was found narrowed and its smooth circular shape was impaired (Figure 1a, b). Smooth muscle cell proliferation, disorganized cellular arrangement, intensive connective tissue increase, and development of intimal hyperplasia were observed in the intimal area (Figure 1c).

The lumen of the right carotid artery of Group B was larger and its geometrical shape was more proper than the lumen of the right carotid artery of Group A. Consequently, the vascular lumen of Group B was larger and smoother (Figure 1b-f). When the right carotid arteries of both groups were compared, intimal hyperplasia and medial hypertrophy were much more in Group A (Figure 1c-h).

Histomorphometric measurements

Luminal diameter

The mean luminal diameter was 490,067±50,972 µm in Group A and 716.018±24.797 µm in Group B. It was significantly larger in Group B (p=0.001) (Table 1).

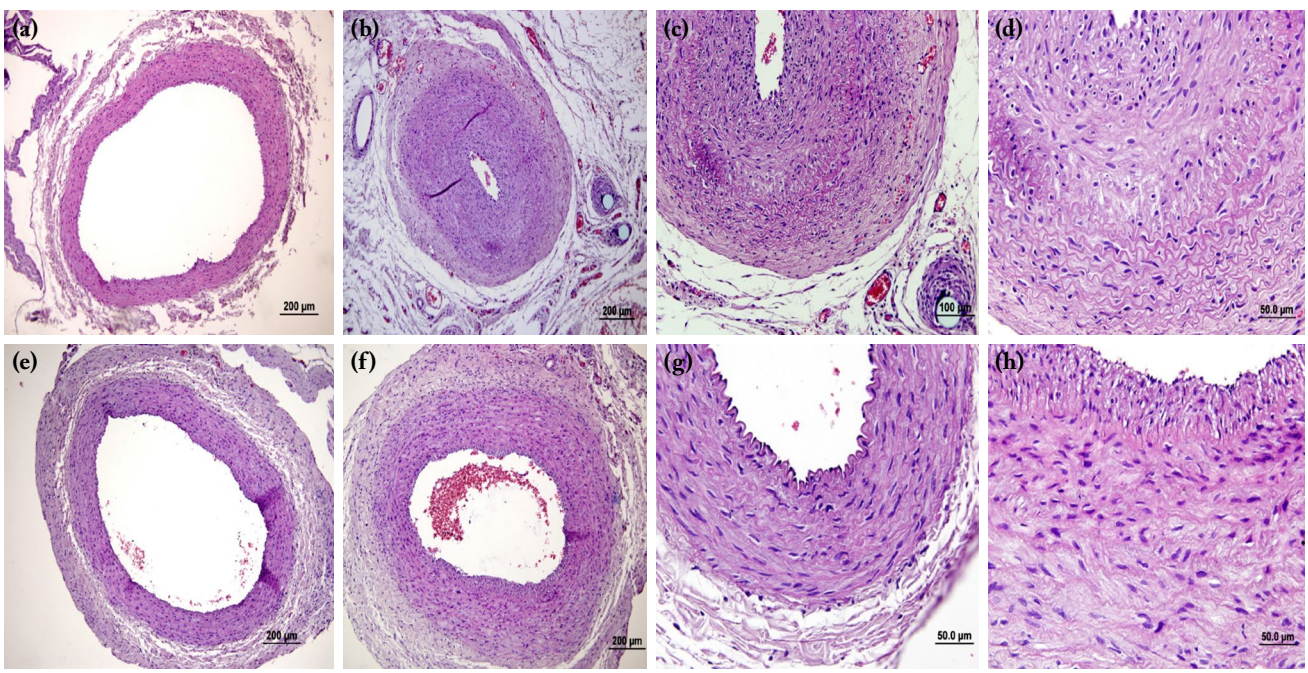

Figure 1. Histological sections of groups. **(a)** Group A, the histological section of the left carotid artery (H&E, ×40). **(b)** Group A, the histological section of the right carotid artery (H&E, ×40). **(c)** Group A, intimal hyperplasia in the right carotid artery (H&E, ×40). **(d)** Group A, media hypertrophy in the right carotid artery (H&E, ×20). **(e)** Group B, the histological section of the left carotid artery (H&E, ×40). **(f)** Group B, the histological section of the right carotid artery (H&E, ×40). **(g)** Group B, intimal hyperplasia in the right carotid artery (H&E, ×10). **(h)** Group B, media hypertrophy in the right carotid artery (H&E, ×40).

Table 1
Comparison of mean lumen diameters

	Anastomosis not performed	Anastomosis performed	
Group	Mean lumen diameter (μm²)±SE	Mean lumen diameter (μm²)±SE	*p*
Group A	874.932±22.003	490.067±50.972	0.001
Group B	828.585±21.966	716.018±24.797	0.009

SE: Standard error.

Table 2
Comparison of mean luminal areas

	Anastomosis not performed	Anastomosis performed	
Group	Mean lumen diameter (μm²)±SE	Mean lumen diameter (μm²)±SE	*p*
Group A	564474.278±67707.555	144087.608±28545.057	0.001
Group B	495509.965±44001.575	366638.070±62509.091	0.115

SE: Standard error.

Table 3
Comparison of mean intimal areas

	Anastomosis not performed	Anastomosis performed	
Group	Mean lumen diameter (μm²)±SE	Mean lumen diameter (μm²)±SE	*p*
Group A	16427.127±2713.660	181500.733±16731.850	0.001
Group B	13684.608±2014.059	51268.378±6535.621	0.001

SE: Standard error.

Table 4
Comparison of intima/media area ratio

	Anastomosis not performed	Anastomosis performed	
Group	Mean lumen diameter (μm²)±SE	Mean lumen diameter (μm²)±SE	*p*
Group A	0.016±0.002	0.295±0.028	0.001
Group B	0.015±0.002	0.061±0.011	0.001

SE: Standard error.

Luminal area

The mean luminal area was 144.087,608±28.545,057 μm² in Group A and 366.638.070±62.509.091 μm² in Group B. It was significantly lower in Group A (p=0.001) (Table 2).

Intimal area

The mean intimal area was 181.500,733±16.731,850 μm² in Group A and 51.268.378±6.535.621 μm² in Group B. It was significantly larger in Group A (p=0.001) (Table 3).

Intima/media area ratio

The intima/media area ratio was significantly lower in Group B (p=0.001) (Table 4).

DISCUSSION

Intimal hyperplasia is a normal adaptive response of arteries against hemodynamic stress and also is an exaggerated healing process after arterial injuries such as bypass grafting, endarterectomy, and balloon angioplasty with or without stenting. Neointimal hyperplasia develops through a complex process including platelet aggregation, leukocyte chemotaxis, VSMC proliferation and migration, ECM alterations, and endothelial cell proliferation.[10]

The intimal response that develops after arterial damage is observed in three stages. Smooth muscle cell proliferation begins in the first 24 hours. After endothelium damage develops, the damaged area is coated with platelets. Following adhesion, platelets release vasoactive and thrombotic factors in their granules (serotonin, adenosine diphosphate, fibrinogen, and Von Willebrand factor) and release growth factors (PDGF, transforming growth factor, and epidermal growth factor). Mitogenic growth factors initiate the proliferation of smooth muscle cells. Proliferated smooth muscle cells in the media layer migrate to the intima and lead to intimal hyperplasia. On Days 3 and 14, these smooth muscle cells migrate to the intima, and neointima and neointimal hyperplasia develop. In the third stage, smooth muscle cells create a layer that results in the narrowing of the vessel lumen rapidly.[11,12]

Cilostazol has many pharmacological effects including vasodilation, inhibition of platelet activation and aggregation, thrombosis inhibition, increased blood flow to the limbs, improvement in serum lipids with the reduction of triglycerides and elevation of high-density lipoprotein cholesterol, and VSMC growth inhibition.[13] Owing to these effects, cilostazol is used to reduce the risk of restenosis and repeat revascularization after percutaneous coronary interventions.[14]

Cilostazol is used for the treatment of peripheral arterial occlusive disease by oral delivery.[15] Systemic administration of cilostazol at 30 mg/kg per oral twice per day was reported to inhibit neointimal formation in balloon-injured rat carotid arteries by 32%.[16]

In a study, Yamamoto et al.[17] showed that locally applied cilostazol inhibited neointimal hyperplasia and medial thickening in a vein graft model. A 1-cm segment of the right femoral vein was harvested and transplanted into the abdominal aorta in an end-to-end fashion. In the cilostazol-treated group, rats with the anastomotic stricture received a topical application of 20 mg of cilostazol dissolved in 200 µL of dimethyl sulfoxide containing 25% Pluronic® gel (Letco Medical, Decatur, AL, USA) around the interposed graft. The rats in the control group received the dimethyl sulfoxide Pluronic® gel without cilostazol. The effectiveness of cilostazol applied locally to implanted vein grafts was demonstrated in suppressing neointimal hyperplasia in this rat model.

Bilateral reversed jugular vein interposition grafts of the common carotid artery were performed in 12 Beagle dogs. Starting from seven days before surgery, either cilostazol (30 mg/day; n=6) or a placebo (n=6) was given orally twice daily. Vein grafts were harvested at Week 1 or Week 4. At Week 1 after implantation, the cilostazol group showed significantly less cell proliferation than the placebo group. At Week 4 after implantation, the intimal and medial thickness was significantly thinner in the cilostazol group than in the placebo group.[18]

Cilostazol is an agent with a pleiotropic mechanism of action and multiple beneficial effects through a combination of vasodilation, platelet inhibition, antiproliferative effect, and lipid-lowering properties. Based on these properties, cilostazol has shown promising effects in the management of atherosclerotic vascular disease in coronary, cerebrovascular, and peripheral arteries.[19]

The primary limitation of our study was the lack of molecular data. In the future, we plan to perform a study on a higher budget and include immunohistochemistry data and oxidative stress parameters.

In conclusion, our study results showed that reduction in the lumen area and diameter after anastomosis were significantly improved in the cilostazol group compared to the control group. The area of intima and intima/media ratio was smaller in the cilostazol group compared to those in the control group, and the difference was statically significant. The medial area of the cilostazol group was significantly higher than the control group. Based on these findings, cilostazol may be useful for

preventing intimal hyperplasia and smooth muscle cell proliferation after vascular surgery.

Ethics Committee Approval: The study protocol was approved by the Dokuz Eylül University Faculty of Medicine Ethics Committee (date: 16.12.2011, no: 69/2011). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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

Author Contributions: Idea/concept, design, critical review: A.C.E.; Data collection and/or processing, writing the article, control/supervision: Ç.B.; Literature review, analysis and/or interpretation, writing the article: U.K.

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Cardiovascular Surgery and Interventions

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Correlation of QRS/T angle with clinical, echocardiographic, and hemodynamic variables in chronic thromboembolic pulmonary hypertension patients

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ABSTRACT

Objectives: In this study, we aimed to examine the relationships between frontal QRS-T (fQRS-T) angle prognostic risk factors outlined in the current pulmonary hypertension (PH) guidelines and to demonstrate whether the fQRS-T could detect patients with unfavorable echocardiographic and hemodynamic data.

Patients and methods: Between July 2009 and February 2023, a total of 33 patients (8 males, 25 females; median age: 61 years; range, 55 to 70 years) with chronic thromboembolic pulmonary hypertension (CTEPH) who underwent electrocardiographic (ECG) examination were retrospectively analyzed. The fQRS-T angle was calculated from surface ECGs. Functional class, 6-min walk distance, and brain natriuretic peptide values were recorded. Two-dimensional echocardiographic data including comprehensive right ventricular (RV) functions, right atrial area (RAA), tricuspid annular systolic plane excursion (TAPSE), systolic pulmonary artery pressure (sPAP), and TAPSE/sPAP ratio were noted. Among invasive hemodynamic variables, sPAP, mean PAP (mPAP), pulmonary vascular resistance (PVR), and cardiac index (CI) were obtained. The correlations between clinical, echocardiographic, and hemodynamic variables were analyzed.

Results: There was no significant correlation between clinical variables and fQRS-T angle. The TAPSE and TAPSE/sPAP ratio were negatively correlated with fQRS/T angle (r=-0.37, p=0.02, r=-0.35, and p=0.03, respectively), whereas RV Tei index and RAA were positively correlated with the fQRS-T angle (r=0.53, p=0.014, r=0.47, and p=0.007, respectively). The hemodynamic data including sPAP, mPAP, and PVR were positively correlated with the fQRS-T angle (r=0.32, p=0.048, r=0.34, p=0.034, r=0.35, and p=0.02, respectively) and CI was negatively correlated with the fQRS-T angle (r=-0.30, p=0.048).

Conclusion: Our study results suggest that the fQRS/T angle is correlated with poor prognostic echocardiographic and hemodynamic variables in CTEPH patients.

Keywords: Chronic thromboembolic pulmonary hypertension, electrocardiography, QRS-T angle.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a possible mortal late consequence of acute pulmonary embolism promoted by ongoing occlusion of the pulmonary arteries (PAs) by organized thrombus, resulting in flow dispersion and alterations in the pulmonary microvasculature. It is the fibrotic transformation of the PA thrombus, which causes constant mechanical obstruction in the PAs and an increase in the flow in the open PA bed.[1] Chronic thromboembolic pulmonary hypertension is an underrecognized and is one of the potentially mortal groups of pulmonary hypertension (PH), if left untreated.[2] The gold-standard treatment of choice in CTEPH patients is pulmonary endarterectomy, which significantly improves invasive hemodynamics.[3]

Various clinical, echocardiographic, and hemodynamic variables are currently been used in risk stratification in Group 1 PH.[4] It has been demonstrated that European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk stratification tool is also appropriate in CTEPH

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patients.[5] Nevertheless, additional more simplified risk assessment tools are warranted in patients with PH.

Electrocardiography (ECG) is a basic, readily accessible diagnostic modality in patients with cardiovascular disease and can mirror the cardiac anatomical and hemodynamic changes induced by PH in terms of cardiac electrical activity in CTEPH patients.

The frontal QRS-T (fQRS-T) angle is expressed as a manifestation of myocardial repolarization and depolarization diversity and is computed by the difference between ventricular depolarization (QRS axis in ECG) and repolarization (T wave).[6] It has been shown that alterations in QRS-T angle correlate with echocardiographic systolic PA pressure (sPAP), right atrial (RA) and right ventricular (RV) size, and impaired RV functions in CTEPH patients.[7]

In the present study, we aimed to examine the relationships between fQRS-T angle prognostic risk factors outlined in the current PH guidelines and to demonstrate whether the fQRS-T could detect patients with unfavorable echocardiographic and hemodynamic data.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Dokuz Eylül University Faculty of Medicine, Department of Cardiology between July 2009 and February 2023. Initially, a total of 81 patients with CTEPH were screened. The diagnosis of CTEPH was made based on an invasively measured mean PA pressure (mPAP) of higher than 25 mmHg and a pulmonary capillary wedge pressure (PCWP) of less than 15 mmHg and perfusion defects as assessed by conventional pulmonary angiography, computed tomography pulmonary angiography and ventilation-perfusion scintigraphy after at least three months of optimal anticoagulation treatment. Electrocardiographic readings were obtained from 43 patients. The ECGs were recorded at the first diagnostic workup of PH patients before echocardiographic examination or right heart catheterization (RHC). Inclusion criteria were age between 18 and 90 years and having a diagnosis of CTEPH. Exclusion criteria were as follows: age <18 or >90 years, having bundle branch block, atrioventricular block, permanent pacemaker, ineligible or missing ECG readings, severe liver failure or chronic renal failure, and active malignancy. Finally, a total of 33 patients (8 males, 25 females; median age: 61 years; range, 55 to 70 years) who met the inclusion criteria were recruited.

Data collection

Institutional medical records were used for demographic, anthropometric, laboratory, ECG, echocardiographic, and hemodynamic data. The laboratory parameters including baseline serum glucose, creatinine, estimated glomerular filtration rate (eGFR), and brain natriuretic peptide (BNP) were recorded.

Electrocardiography

Utilizing a paper rate of 25 mm/sec and a standard deviation of 0.1 mV/mm, a 12-lead ECG was obtained from each patient. Heart rate (HR), PR interval, QRS duration, QT and QTc interval, QRS axis, and T axis were all automatically computed by the ECG machine and examined by a cardiologist. Using the T and QRS axis, the fQRS-T angle was computed. If the computed angle was more than 180 degrees, 360 - [obtained angle] was determined as the fQRS-T angle (Figure 1).

Echocardiography

A Philips HD 11 XE ultrasound system (Philips, Andover, MA, USA) with a 3.2 MHz transducer was used for echocardiographic examination. The RV-focused apical four-chamber (4C) view was used for the linear longitudinal end-diastolic dimension of RV (RVd). The RV fractional area change (RVFAC) was computed as (area at end of diastole - area at the end of systole)/area at end of diastole × 100%.[8] In the apical 4C view, an M-mode cursor was set along the lateral RV wall to the tricuspid annulus. The maximum length of tricuspid annulus movement along systole was specified as tricuspid annular systolic plane excursion (TAPSE). The RA area (RAA) was calculated at the end of the systole from the apical 4C view.

Tissue Doppler imaging was utilized to record the RV systolic (RV S') rate and RV Tei index. The RV Tei index was determined by dividing the ejection period by the summation of the contraction duration and isovolumetric relaxation duration.[8] Continuous-wave Doppler was used for recording tricuspid regurgitation velocity (TRV). The peak TR gradient was computed by the modified Bernoulli equation [4 × TRV2]. The inferior vena cava (IVC) was visualized from

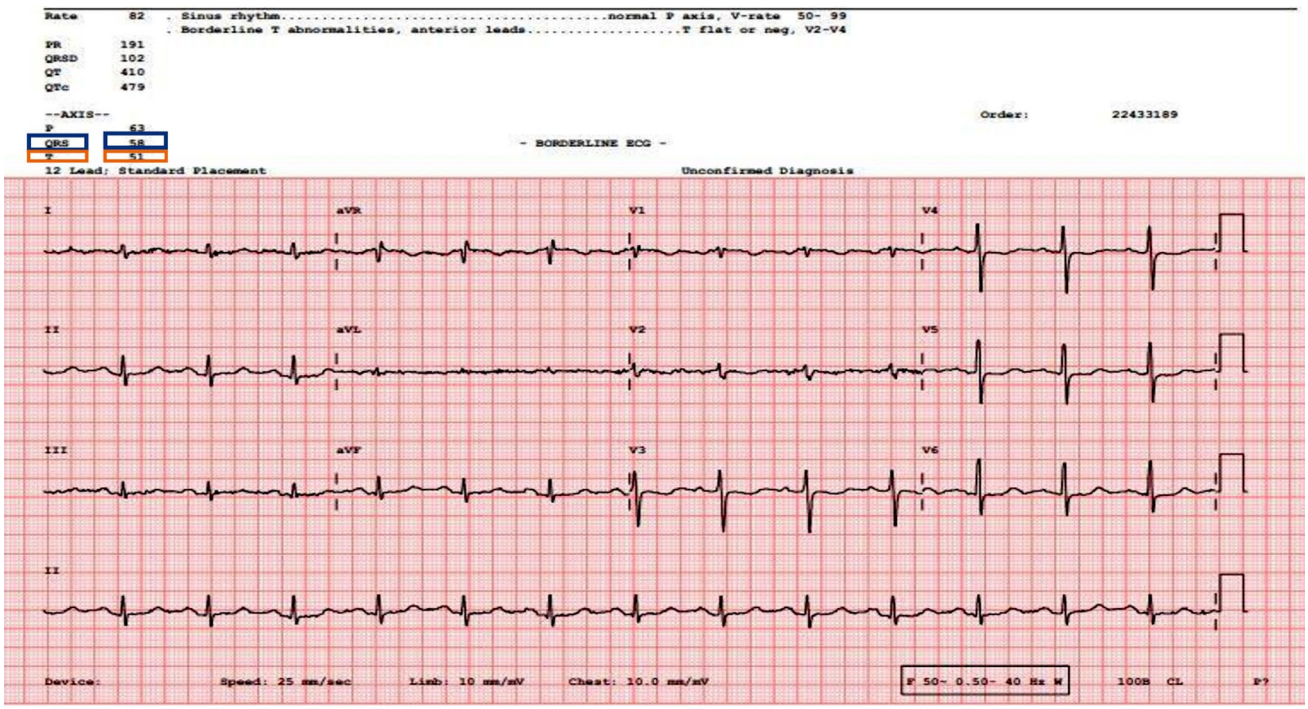

Figure 1. An ECG example showing the measurement of the QRS-T angle. The QRS axis and T axis were all automatically computed by the ECG (arrowheads). Using the T and QRS aqis, the fQRS-T angle was computed. If the computed angle was more than 180 degrees, 360 - [obtained angle] was determined as the fQRS-T angle. For this ECG example, the QRS-T angle is 7° (QRS angle= 58°, T angle= 51°).

ECG: Electrocardiographic; fQRS-T: Frontal fQRS-T.

Table 1
Baseline characteristics of patients

Variables	n	%	Mean±SD	Median	IQR
Age (year)				61	55-70
Sex					
Female	25	75.8			
Body mass index (kg/m^2)			28.8±7.4		
6-minute walk distance (m)				320	120-400
Brain natriuretic peptide (pg/mL)		220	83-450		
Serum glucose (mg/dL)				101	87.5-120.5
Creatinine (mg(dL)				0.8	0.7-1.05
eGFR (mL/min/1.73 m^2)			76.9±25.5		
NYHA functional class					
Class II	9	27.3			
Class III	22	66.7			
Class IV	2	6			
Medications					
Bosentan	2	6			
Macitentan	1	3			
Epoprostenol	1	3			
Treprostinil	1	3			
Riociguat	24	72.7			

SD: Standard deviation; IQR: Interquartile range; eGFR: Estimated glomerular filtration rate; NHYA: New York Heart Association.

the subcostal view, and patients were advised to quickly inhale or "sniff" throughout the procedure. The RA pressure was estimated using the inspiratory magnitude of IVC collapse and the size of the IVC.[9] The sum of RA pressure and anticipated peak TR gradient was recorded as sPAP.

Right heart catheterization

An expert cardiologist conducted RHC using femoral access, while the patient was at rest and without anesthesia. The RA pressure, PCWP, mPAP, diastolic, and systolic PA pressures (dPAP, and sPAP,

Table 2
Electrocardiographic, echocardiographic, and hemodynamic data of the patients (n=33)

	n	%	Mean±SD	Median	IQR
Electrocardiographic data					
Heart rate (bpm)			84±14		
PR interval (msec)			153±38		
QRS duration (msec)				90	87-93
QT interval (msec)			387±36		
QTc (msec)				447	437-464
Frontal QRS-T angle°				47	20-93.5
Echocardiographic data					
RV diameter (mm)			36±7.6		
RV FAC (%)			23.8±8.9		
TAPSE (mm)			17.6±5.4		
RV S' (cm/s)			10.7±3.9		
RV Tei index (%)			46.7±25.9		
Right atrial area (cm^2)			22.1±3.9		
sPAP (mmHg)			70.6±28.1		
TAPSE/sPAP (mm/mmHg)				0.25	0.14-0.39
Tricuspid regurgitation	11	33.3			
Mild	8	24.2			
Moderate	14	42.3			
Severe	3	9.1			
Pericardial effusion					
Hemodynamic data					
sPAP (mmHg)			75.6±24.7		
mPAP (mmHg)			42±12.7		
dPAP (mmHg)				27.5	21.7-31.5
PCWP (mmHg)			12.9±4		
PVR (Woods)			10.3±7.5		
CO (L/min)			3.7±0.9		
CI (L/min/m^2)			2.1±0.6		
RA pressure (mmHg)			11.9±6.9		
MVO^2 (%)			57.8±8.3		

SD: Standard deviation; IQR: Interquartile range; RV: Right ventricle; S': Systolic velocity; FAC: Fractional area change; TAPSE: Tricuspid annular plane systolic excursion; sPAP: Systolic pulmonary artery pressure; mPAP: Mean pulmonary artery pressure; dPAP: Diastolic pulmonary artery pressure; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; CO: Cardiac output; CI: Cardiac index; RA: Right atrium; MVO^2: Mixed venous oxygen saturation.

respectively) were recorded. Blood gas analyses were obtained. The indirect Fick method was used to evaluate cardiac output (CO). Cardiac index (CI) was calculated as CO/body surface area and the pulmonary vascular resistance (PVR) was determined as [mPAP-PCWP]/CO.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). The normality of the continuous data was checked with histograms and the Kolmogorov-Smirnov test. Continuous data were expressed in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. The Pearson and Spearman correlation analyses were used to identify the associations between the fQRS-T angle and clinical, laboratory, echocardiographic, and hemodynamic variables. A *p* value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients are shown in Table 1. Twenty-two (66.7%) patients had New York Heart Association Class III symptoms and 24 (72.7%) patients received riociguat treatment. The median 6-min walk distance was 320 (range, 120 to 400) m and the median BNP was 220 (range, 83 to 450) pg/mL.

Electrocardiographic, echocardiographic, and hemodynamic data of the patients are presented in Table 2. The mean HR was 84±14 bpm and the median fQRS-T angle was 47° (range, 20 to 93.5°) degrees. The mean echocardiographic RAA was 22.1±3.9 cm^2 and the median TAPSE/sPAP ratio was 0.25 (range, 0.14 to 0.39) mm/mmHg. Only three patients (9.1%) had pericardial effusion. The RHC data revealed that the mean RA pressure was 11.9±6.9 mmHg, the mean CI was 2.1±0.6 L/min/m^2, and the mean mixed venous oxygen saturation was 57.8±8.3%.

The correlations between the fQRS-T angle and clinical, laboratory, echocardiographic, and hemodynamic variables are given in Table 3 and Figure 2. Accordingly, there was no significant correlation between the fQRS-T angle and clinical and laboratory characteristics of the patients. Among echocardiographic data, however, TAPSE and TAPSE/sPAP ratio were negatively correlated with fQRS/T angle (r=-0.37, p=0.02, and r=-0.35, p=0.03, respectively), whereas the RV Tei index and RAA were positively correlated with fQRS-T angle (r=0.53, p=0.014, and r=0.47, p=0.007, respectively). The hemodynamic data including sPAP, mPAP, and PVR were positively correlated with fQRS-T angle (r=0.32, p=0.048, r=0.34, p=0.034, and r=0.35, p=0.02, respectively) and CI was negatively correlated with the fQRS-T angle (r=-0.30, p=0.048).

Table 3
The bivariate correlations between the fQRS-T angle and clinical, laboratory, echocardiographic, and hemodynamic parameters

	Frontal QRS-T angle	
	r	*p*
Clinical and laboratory parameters		
NHYA functional class	0.29	0.1
Six-minute walk distance (m)	-0.23	0.2
Brain natriuretic peptide (pg/mL)	0.06	0.7
Echocardiographic parameters		
RV diameter (mm)	0.17	0.29
RV FAC (%)	-0.24	0.24
TAPSE (mm)	-0.37	**0.02**
RV S' (cm/s)	-0.06	0.72
RV Tei index (%)	0.53	**0.014**
Right atrial area (mm^2)	0.47	**0.007**
sPAP (mmHg)	0.26	0.09
TAPSE/sPAP	-0.35	**0.03**
Hemodynamic parameters		
sPAP (mmHg)	0.32	**0.048**
mPAP (mmHg)	0.34	**0.034**
dPAP (mmHg)	0.14	0.41
PCWP (mmHg)	-0.09	0.58
PVR (Woods)	0.35	**0.02**
CO (L/min)	-0.29	0.07
CI (L/min/m^2)	-0.30	**0.048**
RA pressure (mmHg)	0.23	0.15
MVO^2 (%)	-0.15	0.4

fQRS-T: Frontal QRS-T; NHYA: New York Heart Association; RV: Right ventricle; FAC: Fractional area change; TAPSE: Tricuspid annular plane systolic excursion; S': Systolic velocity; sPAP: Systolic pulmonary artery pressure; mPAP: Mean pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; CO: Cardiac output; CI: Cardiac index; RA: Right atrium; MVO^2: Mixed venous oxygen saturation.

DISCUSSION

The present study is a rare report in the current literature to highlight the importance of the fQRS-T angle, which is an ECG sign of myocardial repolarization and depolarization heterogeneity,

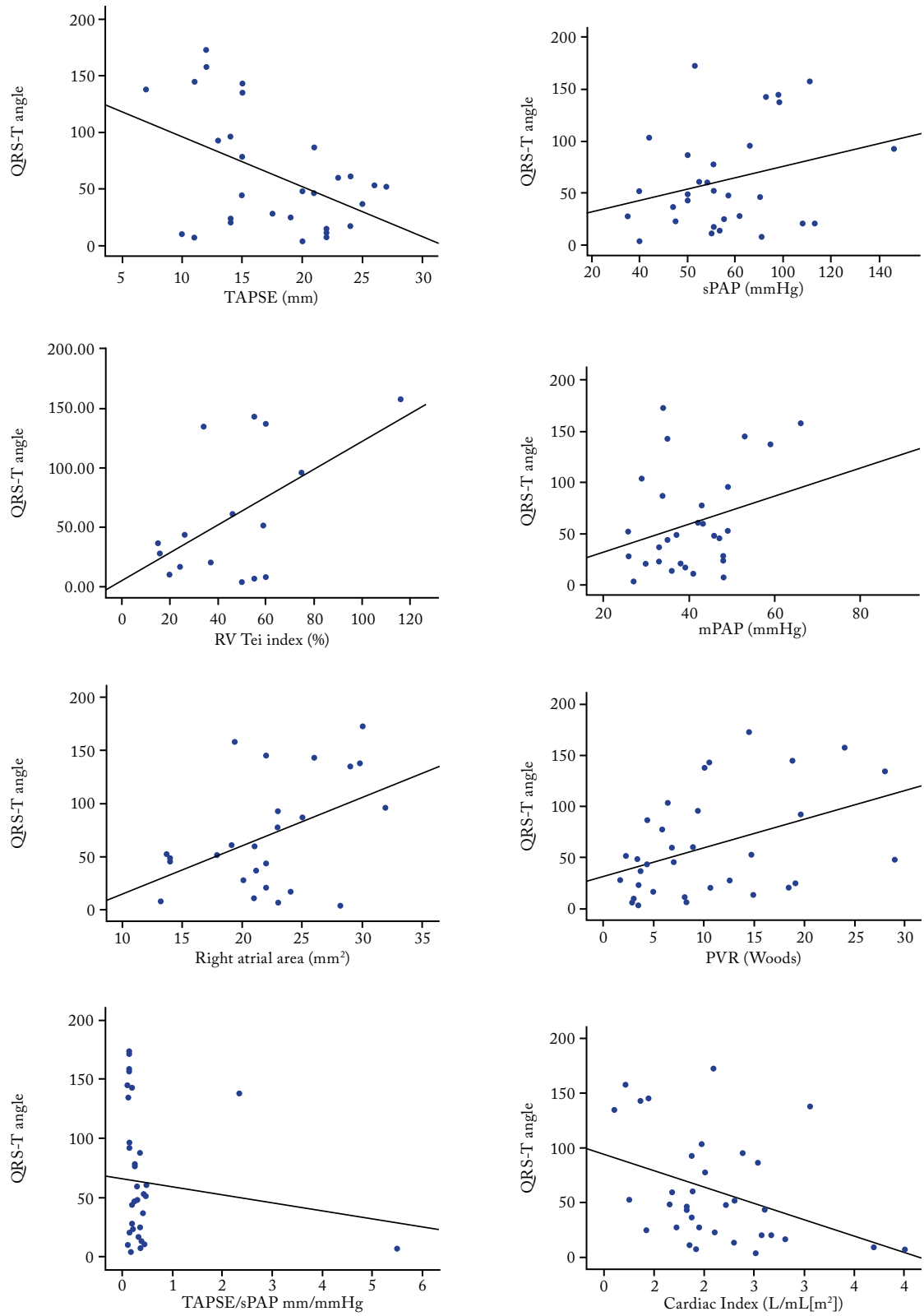

Figure 2. The correlations between the fQRS-T angle and echocardiographic and hemodynamic variables.
fQRS-T: Frontal QRS-T.

and also affects adverse cardiovascular outcomes and overall fatality rates in CTEPH patients. Our study showed that the fQRS-T angle was negatively associated with the TAPSE and TAPSE/sPAP ratio, while it was positively correlated with RV Tei index and RAA in CTEPH patients. Among hemodynamic data, sPAP, mPAP, and PVR correlated positively with the fQRS-T angle, while CI was negatively correlated with the fQRS-T angle. However, there was no significant association between the fQRS-T angle and clinical and laboratory characteristics in patients with CTEPH.

Under normal circumstances, the left ventricular (LV) mass is higher than the RV mass, and RV electrical activity is concealed by LV.[10] Pulmonary hypertension results in RV pressure overload and RV hypertrophy. As RV mass increases, RV contributes to ventricular depolarization and QRS axis changes. The course of the T-axis becomes divergent to QRS-axis and the spatial QRS-T (sQRS-T) angle increase with elevated PH.[11] It was previously shown that, even in the very early phases of PH, the sQRS-T angle was elevated in rats.[10] Henkens et al.[12] also demonstrated that the sQRS-T angle was greater in patients with chronically elevated RV pressure compared with controls.

In the current study, we investigated the clinical, echocardiographic, and invasive hemodynamic correlates of fQRS-T angle CTEPH patients. We were unable to demonstrate a correlation between clinical variables and fQRS-T angle in patients with CTEPH. The inadequate significance can be attributed to the small sample size used in our study. However, we were able to find significant associations between echocardiographic variables including TAPSE, TAPSE/sPAP ratio, RV Tei index, and RAA and fQRS-T angle. Previously, similar to our findings, the QRS-T angle was demonstrated to be linked to echocardiographic variables such as SPAP, dimension of RA and RV, and RV systolic dysfunction and impaired diastolic function in patients with CTEPH.[7] We showed that the fQRS-T angle was negatively associated with TAPSE and TAPSE/sPAP ratio. As TAPSE estimates RV contractile function, an increase in fQRS-T angle CTEPH patients may correspond to RV systolic dysfunction. Recently, a new prognostic parameter was included in the current PH guidelines. The TAPSE/sPAP ratio, which is a surrogate non-invasive marker of RV-PA coupling and provides information about RV diastolic function, was demonstrated to be a significant prognostic variable in PH patients.[13,14] An increase in the fQRS-T angle was also found to be linked to a reduction in TAPSE/sPAP ratio in our study. Therefore, we can speculate that an increase in fQRS-T angle in patients with CTEPH may correspond to impaired both RV diastolic and systolic function. Another parameter that reflects the overall function of the RV is the RV Tei index. The RV Tei index has been shown to be increased in patients with connective tissue-associated-PAH due to RV diastolic dysfunction and decreased myocardial contractility of RV.[15] Similarly, we showed that the RV Tei index was elevated in CTEPH patients and an elevation in the fQRS-T angle corresponded to an increase in RV Tei index of CTEPH patients. Additionally, RAA has been shown to be a valuable prognostic factor in PH patients. The mortality of PH patients increases in patients with elevated values of RAA.[4] In the current study, an increase in fQRS-T angle was linked to an increase in RAA. Our results are consistent with the findings of Sakhnova et al.[7] showing that the QRS-T angle is related to elevated RA size.

In this study, we also examined the correlations between the fQRS-T angle and invasive hemodynamic data in CTEPH patients. The sPAP, mPAP, and PVR correlated positively, whereas CI was negatively correlated with the fQRS-T angle. The positive correlation between sPAP, mPAP, and PVR and fQRS-T angle is comprehensible as an increase in PA pressures and PVR results in an increase in RV mass and a change in QRS and T-axis, resulting in an increased QRS-T angle.[11] Chronic pressure and volume overload on RV in patients with PH modify the geometry of RV. As a result, RV occupies more space in the pericardium and causes paradoxical interventricular septum movement, thereby leading to a decrease in LV volume at end-diastole.[16] The decrease in LV diastolic volume at end-diastole results in altered LV stroke volume as explained by the Frank-Starling mechanism.[17] This may explain the negative correlation between CI and fQRS-T angle.

Nonetheless, this study has several limitations. First, our study has a single-center, retrospective design. Second, since CTEPH is a rare condition, the number of patients is limited. Although multi-center studies involving more patients on this subject are needed, we believe that our study may be a pioneer for further studies on this subject. In addition, although we have long-term follow-up data, the impact of the

fQRS-T angle on prognosis in CTEPH patients is unclear due to the small number of subjects. Another limitation of our study was the utilization of an fQRS-T angle instead of an sQRS-T angle. However, the fQRS-T angle has been used instead of the sQRS-T angle in studies on cardiovascular diseases. The main reason for this is that sQRS-T angle measurement is complicated and necessitates sophisticated computer programs. On the contrary, the fQRS-T angle can be simply calculated from the automatic description of the ECG machine.

In conclusion, ECG seems to be a tool that should not be ignored in the evaluation of CTEPH patients. In these patients, the fQRS-T angle, which can be computed simply by ECG, is negatively correlated with TAPSE, TAPSE/sPAP ratio, and CI, while it is positively correlated with RV Tei index, RAA, sPAP, mPAP, and PVR, which are important prognostic factors in patients with PH.

Ethics Committee Approval: The study protocol was approved by the Dokuz Eylül University Faculty of Medicine Ethics Committee (date: 29.03.2023, no: 2023/10-14). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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

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

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Outcomes of preoperative fragmented QRS detection on operative and postoperative events in patients undergoing elective coronary artery bypass grafting

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ABSTRACT

Objectives: This study aims to investigate the preoperative electrocardiographic data of patients who were candidates for elective coronary artery bypass grafting (CABG) in terms of fragmented QRS (fQRS) presence and to evaluate short-term outcomes of fQRS on operative and postoperative courses.

Patients and methods: Between January 2019 and April 2022, a total of 178 patients (137 males, 41 females; mean age: 61.4±9.3 years; range, 39 to 85 years) who underwent elective CABG were retrospectively analyzed. Preoperative electrocardiographic examinations were performed to detect fQRS. The patients were divided into two groups according to presence of fQRS as the fQRS+ (n=35) and fQRS– (n=143) group. Demographic, clinical, laboratory, operative, and postoperative data of both groups were evaluated.

Results: The mean duration of cardiopulmonary bypass (p=0.017) and number of CABG (p=0.026) in the fQRS group were found to be significantly higher, while the mean preoperative left ventricular ejection fraction values were lower in this group (p<0.001). There was a significant increase in the left ventricular ejection fraction values at the postoperative third month in the fQRS+ group (p<0.001). Mortality encountered in 5.7% in the fQRS+ group, while this rate was 2.7% in the fQRS– group (p=0.336).

Conclusion: Preoperative detection of QRS fragmentations on admission electrocardiograms may have an additional value in predicting postoperative cardiac status and short-term prognosis in patients undergoing CABG.

Keywords: Atrial fibrillation, coronary artery bypass grafting, coronary vessels, myocardial contraction.

Fragmented QRS (fQRS) is a depolarization disorder that can be detected on a 12-lead surface electrocardiography (ECG) and indicates local myocardial fibrosis.[1] The fQRS was first described by Flowers et al.[2] in 1969 as the appearance of an additional R wave (R′) in relation with an important coronary artery region, or notching in the S wave, or the presence of >1 R′ (fragmentation) in two adjacent ECG diversions. In 1973, Boineau and Cox[3] described fragmentary bipolar potentials secondary to coronary ischemia in an animal experiment. In general, the fQRS is defined as a notching in the R wave, a notching in the S wave, RSR′ pattern or more than one R′ in at least two consecutive leads corresponding to the myocardial tissue which is vascularized by the major coronary arteries. Myocardial fibrosis leads to conduction delays which causes non-homogeneous ventricular depolarization, resulting in a notching of the QRS complex on ECG. The fQRS is a finding associated with an increased cardiovascular risk due to coronary artery disease (CAD).[4] Several studies have shown an association between the increase in the number of leads with fQRS and the degree of myocardial fibrosis, cardiovascular morbidity, and mortality.[5]

Coronary artery disease is one of the leading causes of cardiovascular morbidity and mortality. It is responsible for about 30% of mortality over the age of 35 in developed countries.[6] Coronary artery bypass grafting (CABG) is one of the most common procedures to treat CAD.[7] In the present study, we aimed to investigate the effects of fQRS on operative

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and postoperative courses in patients undergoing elective CABG, to identify the cardiovascular risk profiles of the patients, and to identify the need for closer follow-up in post-CABG patients.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Medicana International Istanbul Hospital, Department of Cardiovascular Surgery between January 2019 and April 2022. A total of 178 patients (137 males, 41 females; mean age: 61.4±9.3 years; range, 39 to 85 years) who underwent elective CABG during the study period were included. Exclusion criteria were as follows: having pacemakers, undergoing emergent CABG, and previous valve surgery. A 12-lead ECG was performed preoperatively in all patients with a filtration rate of 0.15 to 100 Hz, AC filtration of 60 Hz, 25 mm/h speed, 10 mm/mV amplitude settings in the supine position. All ECGs were evaluated for the presence of QRS by two cardiologists who were blinded to the study design. The QRS fragmentation was defined on a 12-lead ECG as an additional R wave (R′), notching on a R or S wave, RSR pattern or multiple R′s on two adjacent leads with or without a Q wave on the QRS wave. According to the presence of fQRS on surface ECG, the patients were divided into two groups as the fQRS+ (n=35) and fQRS– (n=143) group. Demographic characteristics of the patients such as age, sex, body mass index (BMI) and clinical data such as comorbidities were recorded. Both groups were compared in terms of high-sensitivity C-reactive protein (hs-CRP), lipid profile, complete blood count parameters, left ventricular ejection fraction (LVEF) values on transthoracic echocardiography, cardiopulmonary bypass (CPB) duration, number of CABG, aortic clamp time (ACT), duration of intubation, length of intensive care unit (ICU) stay and hospital stay, postoperative new-onset atrial fibrillation (POAF), and mortality rates.

Statistical analysis

Statistical analysis was performed using the R version 4.2.0 software (R Core Team; R Foundation for Statistical Computing, Vienna, Austria). Continuous data were presented in mean ± standard deviation (SD) or median (min-max), while categorical data were presented in number and frequency. The compatibility of quantitative data with normal distribution was examined using the Shapiro-Wilk test. In terms of quantitative data, the Student t-test or Mann-Whitney U test was used for the comparisons of the groups. In terms of categorical data, the chi-square test or Fisher exact test was used to compare the groups. To predict the presence of fQRS, area under curve (AUC), sensitivity and specificity values and 95% confidence intervals (CIs) under the receiver operating characteristics (ROC) curve were used and the diagnostic accuracy of significant variables in the univariate analysis was examined. The most optimal cut-off value was determined, as the value corresponding to the maximum Youden index (J=Sensitivity+Specificity-1). Postoperative risk factors for the presence of fQRS were determined in the univariate logistic regression model and multiple logistic regression model was further applied. The odds ratio (OR) values obtained from the models and the corresponding 95% CI values were presented. The "pROC" library was used in the *R* program (by Xavier Robin, Switzerland) for ROC analysis. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 178 patients included in the study, the fQRS was detected in 35 (19.6%) patients. Demographic, clinical, laboratory, operative and postoperative data of both groups are summarized in Table 1. On transthoracic echocardiography performed before elective CABG, the mean left LVEF values of the patients with fQRS+ were 41.51±10.96% (range, 28 to 60%) (p<0.001). The mean neutrophil/lymphocyte ratios were found 2.73±2.32 (range, 0.71 to 20.8), whereas the mean platelet/lymphocyte ratios were 126.89±124.32 (range, 39.19 to 1481.2) and the mean eosinophil/lymphocyte ratios were 0.09±0.08 (range, 0.002 to 0.578), respectively.

All patients in the study received a standard CABG anesthesia. Sternotomy was performed in all patients. Left internal mammary artery and great saphenous vein grafts were prepared. The patients were operated under CPB and under cardioplegic arrest. The mean number of CABG in the fQRS+ group was 4.71±0.99 (range, 1 to 8) (p=0.026). The mean CPB duration was 135.46±27.64 (range, 28 to 192) min and the mean ACT was 67.2±17.94 (range, 20 to 109) min. The diagnostic accuracy of the variables in predicting the presence of fQRS is summarized in Table 2 and Figures 1 and 2. Five (14%) patients needed inotropic support

Table 1
Demographic, clinical, laboratory, operative, and postoperative data of patients

	fQRS + (n=35)				fQRS – (n=143)				
	n	%	Mean±SD	IQR	n	%	Mean±SD	IQR	*p*
Age (year)			60.94±9.37	39-85			61.8±9.18	43-83	0.625‡
Sex									0.069†
Male	31	88.5			106	74.1			
Female	4	11.5			37	25.9			
BMI (kg/m^2)			28.31±4.24	21.56-39.33			29.13±4.55	18.67-41.52	0.254*
Diabetes mellitus	21	60			54	37.7			0.106†
Hypertension	17	48.5			64	44.7			0.684†
LDL (mg/dL)			150.5±32.85	91-289			144.31±33.47	100-240	0.280*
Triglyceride (mg/dL)			222.19±154.74	43-1279			216.6±106.45	101-707	0.487*
Preoperative LVEF (%)			41.51±10.96	28-60			52.14±8.54	30-68	<0.001*
Postoperative 3rd month LVEF (%)			52.06±10.99	36-70			57.38±6.15	36-70	<0.001*
N/L			2.73±2.32	0.71-20.8			2.81±1.46	1.04-6.98	0.205*
P/L			126.89±124.32	39.19-1481.2			108.03±41.39	45.39-233.65	0.428*
E/L			0.09±0.08	0.002-0.578			0.07±0.06	0.013-0.267	0.335*
hs-CRP (mg/L)			8.8±16.74	0.2-88.12			6.21±8.91	1-40.91	0.577*
Number of coronary artery bypass grafts			4.71±0.99	1-8			4.22±1.18	2-7	0.026*
CPB duration (min)			135.46±27.64	28-192			119.63±30.73	26-187	0.017*
ACT (min)			67.2±17.94	20-109			60.97±16.87	40-126	0.074*
Inotrop need after CPB	5	14.2			9	6.3			0.155¶
POAF	3	8.5			3	2.1			0.091¶
Duration of intubation (h)			9.19±13.46	6-168			16.51±28.61	6-144	0.072*
Duration of ICU (day)			2.46±1.4	2-9			2.15±0.84	2-10	0.020*
Duration of in-hospital stay (day)			5.51±2.65	5-18			5.79±1.48	5-20	0.010*
Mortality	2	5.7			4	2.7			0.336¶
Follow-up (month)			12.31±6.74	7-24			13.54±7.84	8-24	0.425*

fQRS: Fragmented QRS; SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction; N: Neutrophil count; L: Lymphocyte count; P: Platelet count; E: Eosinophil count; hs-CRP: High-sensitivity C-reactive protein; CPB: Cardiopulmonary bypass; ACT: Aortic clamping time; POAF: Postoperative new-onset atrial fibrillation; ICU: Intensive care unit; p value extracted from ‡ Student t-test; † Chi-square test; * Mann-Whitney U test (U); ¶ Fisher exact test.

after CPB in the fQRS+ group. The mean duration of intubation in the fQRS+ group after CABG was 9.19±13.46 (range, 6 to 168) h. The mean

Table 2
The diagnostic accuracy of the variables in predicting the presence of fQRS

	fQRS +		fQRS –			AUC (95% CI)			Sensitivity (95% CI)		Specificity (95% CI)	
	Mean±SD	IQR	Mean±SD	IQR	Cut-off point	Mean±SD	IQR	*p*	Mean±SD	IQR	Mean±SD	IQR
CPB duration (min)	135.46±27.64	28-192	119.63±30.73	26-187	≥97.5	0.631	0.533-0.729	0.017	1	1-1	0.211	0.144-0.278
Number of coronary artery bypass grafts	4.71±0.99	1-8	4.22±1.18	2-7	≥3.5	0.616	0.522-0.71	0.026	0.971	0.916-1	0.224	0.155-0.292
Preoperative LVEF (%)	41.51±10.96	28-60	52.14±8.54	30-68	≤46.5	0.784	0.688-0.881	<0.001	0.686	0.532-0.84	0.881	0.828-0.934
Postoperative LVEF (%)	52.06±10.99	36-70	57.38±6.15	36-70	≤57.5	0.784	0.698-0.871	<0.001	0.629	0.468-0.789	0.817	0.753-0.881

fQRS: Fragmented QRS; AUC: Area under curve; CI: Confidence interval; CPB: Cardiopulmonary bypass; LVEF: Left ventricular ejection fraction.

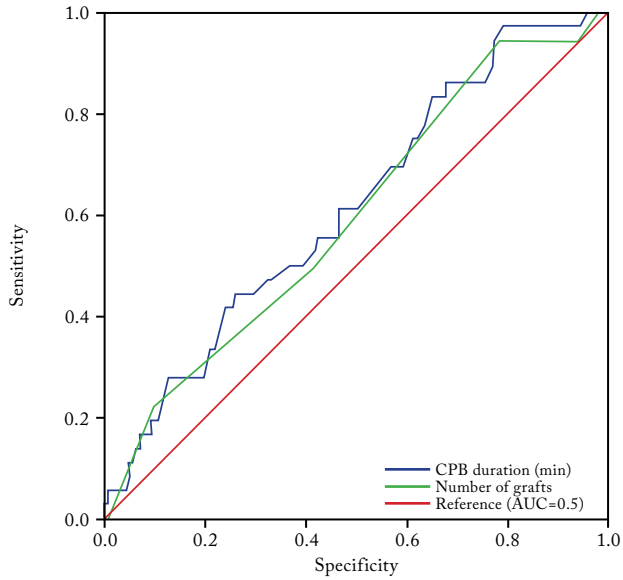

Figure 1. Diagnostic accuracy of values in predicting the presence of fQRS-ROC curve. High values predict the presence of QRS fragmentation.

CPB: Cardiopulmonary bypass; AUC: Area under curve; ROC: Receiver operating characteristics.

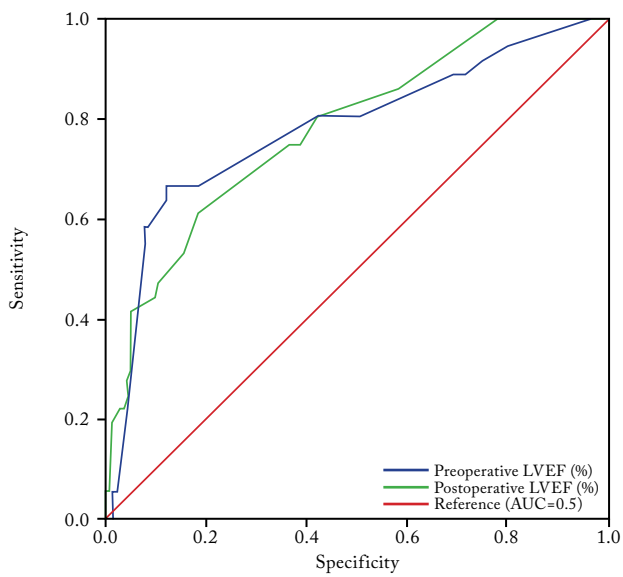

Figure 2. Diagnostic accuracy of values in predicting the presence of fQRS - ROC curve. Low values predict the presence of QRS fragmentations.

LVEF: Left ventricular ejection fraction; AUC: Area under curve; ROC: Receiver operating characteristics.

length of ICU stay and hospital stay was 2.46±1.4 (range, 2 to 9) days (p=0.020) and 5.51±2.65 (range, 5 to 18) days (p=0.010), respectively. Three (8.5%) patients developed in the fQRS+ group. Overall, the postoperative mortality rate was 3.3% (n=6). Mortality was observed within the first 30 days postoperatively. Three (1.7%) patients died from cerebrovascular diseases (CVD), two (1.1%) from pneumoniae, and one (0.55%) from pulmonary embolism. There were two mortality cases in the fQRS+ group, and both patients died from CVD.

Overall, the mean follow-up was 12.31±6.74 (range, 7 to 24) months. The mean LVEF values of the patients in the fQRS+ group at three months were 52.06±10.99% (range, 36 to 70%) (p<0.001).

DISCUSSION

In the present study, we investigated whether the detection of fQRS complexes on ECG in preoperative evaluations of patients undergoing elective CABG was a predictor to determine postoperative cardiac status, short-term prognosis, and mortality. Our study results showed that the duration of CPB (p=0.017), the number of CABG (p=0.026), length of ICU stay (p=0.020), and length of hospital stay (p=0.010) in the fQRS+ group were statistically significantly higher, while preoperative LVEF values were statistically significantly lower (p<0.001). The increase at the postoperative third month in the LVEF values in these patients was statistically significant (p<0.001). However, there was no statistically significant difference between the neutrophil/lymphocyte and hs-CRP values in the fQRS+ group. Hypertriglyceridemia, diabetes mellitus, and hypertension were not statistically significantly different between the groups. Additionally, no statistically significant difference was observed in the rate of POAF, the most common arrhythmia after CABG. The prevalence of fQRS was more common in male patients in our study, whereas increasing age and BMI did not affect the prevalence of fQRS.

Coronary artery bypass grafting is frequently utilized in the treatment of CAD.[8] Although long-term survival is satisfactory after CABG, arrhythmia, need for recurrent myocardial revascularization, cerebrovascular events, sudden death and heart failure may be encountered in approximately one-third of patients in the postoperative follow-up.[9-11] The presence of preoperative fQRS is frequently associated with decreased myocardial contractility and multiple coronary artery occlusions, as evidenced by a decrease in LVEF.[12] It has been shown that patients with preoperative fQRS have significantly lower LVEF values.[13-15] In addition, unlike previous studies, the increase in LVEF at three months after CABG in patients with fQRS+ was statistically significant in our study. Neutrophil/lymphocyte, platelet/lymphocyte, and eosinophil/lymphocyte ratios, and hs-CRP in patients with fQRS+ provided valuable data, particularly following acute coronary syndrome.[16,17] In our study, there was no statistically significant difference in the rate of activated neutrophils, which are the first and most commonly detected white blood cell subtype in damaged myocardial tissue in patients with fQRS, and furthermore lymphocyte count were not also quantifying a diagnostic accuracy, either. Furthermore, there were no significant changes in hs-CRP values, platelet/lymphocyte and eosinophil/lymphocyte ratios in our study.

Postoperative new-onset atrial fibrillation, the most common arrhythmia after CABG, is observed in nearly 10 to 40% of cases.[18] Early and late postoperative POAF increases morbidity.[19] The first study in the literature on the presence of preoperative fQRS to be a significant risk factor for new-onset POAF after CABG was published by Çetin et al.[20] Also, Keskin and Kurtul[21] showed that POAF rate and in-hospital mortality rate were higher in patients with fQRS. However, our study indicates that the presence of preoperative fQRS does not have a statistically significant effect on the development of new-onset POAF.

The QRS fragmentation may be an indicator of early myocardial injury preceding the appearance of fibrosis and scar, and may be used for risk stratification in patients with CAD.[22] Considering the link between multiple critical CAD and fQRS, the increase in the number of CABG and the consequently prolonged CPB durations have gained importance. We consider that revascularization of patients with fibrosis secondary to myocardial ischemia and detection of fQRS in which scar formation is etiologically prominent should be treated with CABG. Preoperative 12-lead ECG is an important diagnostic method in determining morbidity and mortality after CABG. The effects of rhythm disturbances such as long QT interval, T wave

alternance, P wave dispersion and atrial fibrillation, which can be detected by 12-lead ECG, on mortality and morbidity after CABG have been investigated in the literature.[23-25] However, short- and long-term effects of fQRS on morbidity and mortality after CABG have not been examined thoroughly, paving the way for us to conduct the current study. Based on these results, the presence of fQRS is an important marker of morbidity and mortality in post-CABG due to inter- and intraventricular conduction abnormalities secondary to myocardial fibrosis.

The single-center, retrospective design of this study is the main limitation. Although our results showed that fQRS could be a predictor for short-term outcomes, further long-term studies are needed to elucidate the effects of the presence of preoperative fQRS on postoperative course following CABG.

In conclusion, the QRS fragmentation on a 12-lead surface ECG has recently gained increasing attention as a simplified non-invasive ECG marker with diagnostic and prognostic value in CAD. It is a very simple method to evaluate patients who are scheduled for elective CABG with a significant predictor in terms of morbidity and mortality that may be encountered in the early postoperative period. Detection of QRS fragmentations is also a cost-effective method to identify patients who would need close follow-up and treatment in the postoperative period. With the detection of fQRS in patients to be treated with elective CABG, patient groups at a higher risk category can be identified. Patients with fQRS regarding fibrosis secondary to myocardial ischemia should be treated with CABG. The QRS complex fragmentations detected on ECG at the time of initial admission may be useful to identify patients at high cardiovascular risk who would need closer follow-up and treatment after CABG.

Ethics Committee Approval: This was a retrospective and single-center study which was approved by the Medicana International Istanbul Hospital Ethics Committee (date: 12.08.2022, no: 2022/041) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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

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

Author Contributions: Idea/concept, design, data collection and/or processing, analysis and/or interpretation, literature review, writing the article: B.Ş.; Analysis and/or interpretation, critical review: G.G.; Literature review, critical review: A.Ö.

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Cardiovascular Surgery and Interventions

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Comparison of the cardioprotective effects of St. Thomas and del Nido cardioplegia

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ABSTRACT

Objectives: This study aimed to histopathologically examine the cardioprotective effects of St. Thomas and del Nido (DN) cardioplegia.

Materials and methods: A total of 18 rabbits aged 23 weeks and weighing 2000 g were included in the experimental animal study. The animals were randomized to three groups, with six rabbits in each group. The first group was determined as the control group and no cardioprotective agent was given after ligation of the aorta. The rabbits in the second group received DN cardioplegia solution, and those in the third group received the St. Thomas cardioplegia solution. The groups were histopathologically graded and evaluated with six different scores.

Results: There were statistically significant differences between St. Thomas, DN, and control groups with hematoxylin and eosin, caspase 3 and connexin 43 staining at 30, 60, and 90 min ($p<0.05$). However, the St. Thomas, DN, and control groups showed equal score 2- and score 3-weighted, score 3-weighted, and score 3-weighted distributions with connexin 43 at 90 min, respectively; there was no statistically significant difference between the groups ($p=0.144$).

Conclusion: The most adverse tissue damage observed were localized hemorrhage and localized necrosis areas at the end of 90 min of cellular damage. Both cardioplegia applications significantly reduced tissue loss compared to the control group. However, we believe that DN cardioplegia has a longer application time and has better protection.

Keywords: Cardiac protection, cardiac surgery, cardioplegia, del Nido, St. Thomas.

Cardiovascular diseases are among the leading causes of death. The treatment of some of these diseases has only a surgical option. Open heart surgery was introduced in the 1950s. With the discovery of heparin, surgeries were accelerated, and they became more common with the development of the heart-lung machine. Solutions used to stop the heart during open heart surgery are called cardioplegia solutions. There are many types of cardioplegia solutions based on their content. The content and cardioprotective effect of each solution is different.[1]

The content of del Nido (DN) cardioplegia is 1000 mL liquid containing magnesium chloride $6H_2O$ 0.030%, potassium chloride 0.037%, sodium acetate $3H_2O$ 0.37%, sodium chlorid 0.53%, sodium gluconate 0.5%, potassium phosphate monobasic 0.00082%, sodium phosphate dibasic 0.012%, 20% mannitol 17 mL, 15% magnesium sulfate 14 mL, 8.4% (1 mEq/L) sodium bicarbonate 13 mL, 7.5% (1 mEq/L) potassium chloride 26 mL, and 2% lidocaine 6.5 mL. The dose can be given as 20 mL/kg. The cardioprotective effect of the DN solution is longer (90 to 120 min), and it provides better protection. The content of St. Thomas cardioplegia is 110 mEq/L sodium, 16 mEq/L potassium, 2.4 mEq/L calcium, and magnesium. Its duration of action is shorter, and it should be repeated every 20 to 30 min.[2]

Cardiomyocyte death occurs by necrosis or apoptosis. *In vivo* animal studies revealed that caspase 3 and membrane attack complex are among the earliest markers of cell death.[3] Caspase 3 protease degrades several proteins important for cell death signaling (intrinsic or extrinsic apoptosis).[3]

Functional markers are important for normal cardiomyocyte function or maintenance of cardiac

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tissue structural integrity. The best-known functional markers include myoglobin, troponins, creatine kinase, and various cytoskeletal proteins. Connexin 43 (Cx43) is the predominant link in the cardiac cavity junction channels. These channels provide intercellular exchange with ions and small regulatory molecules. Thus, it provides electrical propagation between cardiomyocytes and synchronized heart contractions. Minor Cx43 phosphorylation differences (one of the changes associated with ischemia-induced dissociation) are evident 15 min after the onset of ischemia.[3]

Inflammation is activated to clear the damaged myocardium. Damaged cardiomyocytes diffuse into the extracellular space with the damage-associated molecular pattern, also known as alarm or distress signals. Recent inflammatory markers include S100A8/9, also known as MRP8/14 and calprotectin, interleukin (IL)-6, IL-1β, IL-1α, IL-1 receptor-activated kinase 1, chemokine ligand 2, also known as macrophage inflammatory protein 2, and chemokine ligand 2, also known as MCP-1. Among the earliest *in vivo* inflammatory changes investigated in the human myocardium are S100A8/9, IL-6, and IL-1β.[3]

The histopathological effect of both methods on the heart has not been demonstrated. Hence, this study aimed to histopathologically examine the cardioprotective effects of St. Thomas and DN cardioplegia.

MATERIALS AND METHODS

A total of 18 rabbits aged 23 weeks and weighing 2000 g were included in the experimental animal study. The animals were randomized to three groups, with six rabbits in each group. Standard feed and water were given to the animals that were kept at room temperature (20 to 25°C) with a 12-h dark/light cycle until the experiments.

The first group was determined as the control group and no cardioprotective agent was given after ligation of the aorta. The rabbits in the second group received DN cardioplegia solution, and those in the third group received the St. Thomas cardioplegia solution.

After the protocol, each rabbit was given intraperitoneal anesthesia with a mixture of 10% ketamine 90 mg/kg and 2% xylazine 15 mg/kg. Cold cardioplegia was used in every group (4°C). The dose of cardioplegia was 20 mL/kg for every group. Cardioplegia was applied in 3 to 5 min. In the St. Thomas group, cardioplegia was given every 20 min till the end time (90 min) and once in the DN group. External cold materials were not utilized after applying cardioplegia. After the measurement of body weight, the rabbits were sacrificed by exsanguination. Samples were taken after cardiac arrest since our main goal in this study was to calculate the cardioprotective effect of the cardioplegia solutions. Reperfusion was not evaluated. Heart tissue samples were collected as 30, 60, and 90 min and sent to the histology and embryology laboratory within %10 formaldehyde. Figure 1 demonstrates tissue collection from the animals.

Histological evaluation of heart tissues

Tissue samples collected from all groups were kept in %10 formaldehyde. At the end of 72 h, a histological tissue treatment method was applied to these tissues, and after paraffin blocking, 5 µm serial sections were taken for the histological evaluation of the heart tissue. The sections were stained with hematoxylin and eosin (H&E). The images were examined with the Olympus BX-51 light microscope (Olympus, Tokyo, Japan) and Olympus PP72 Digital Camera (Olympus, Tokyo, Japan) and recorded and scored histologically. The groups were histopathologically graded using the evaluation method of Zhu et al.[4] with six different scores: score 0, natural histopathological appearance; score 1, patchy eosinophilic changes; score 2, localized hemorrhage with localized eosinophilic changes; score 3, localized areas of necrosis; score 4, diffuse hemorrhage with diffuse eosinophilic changes; score 5, diffuse liquefaction necrosis.

Statistical analysis

Data obtained in this study was analyzed using the IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA) software. The chi-square test was used for the comparison of categorical variables between the groups. A p-value <0.05 was considered statistically significant.

RESULTS

When the scoring of H&E staining according to time was examined, it was observed that the St. Thomas, DN, and control groups showed score

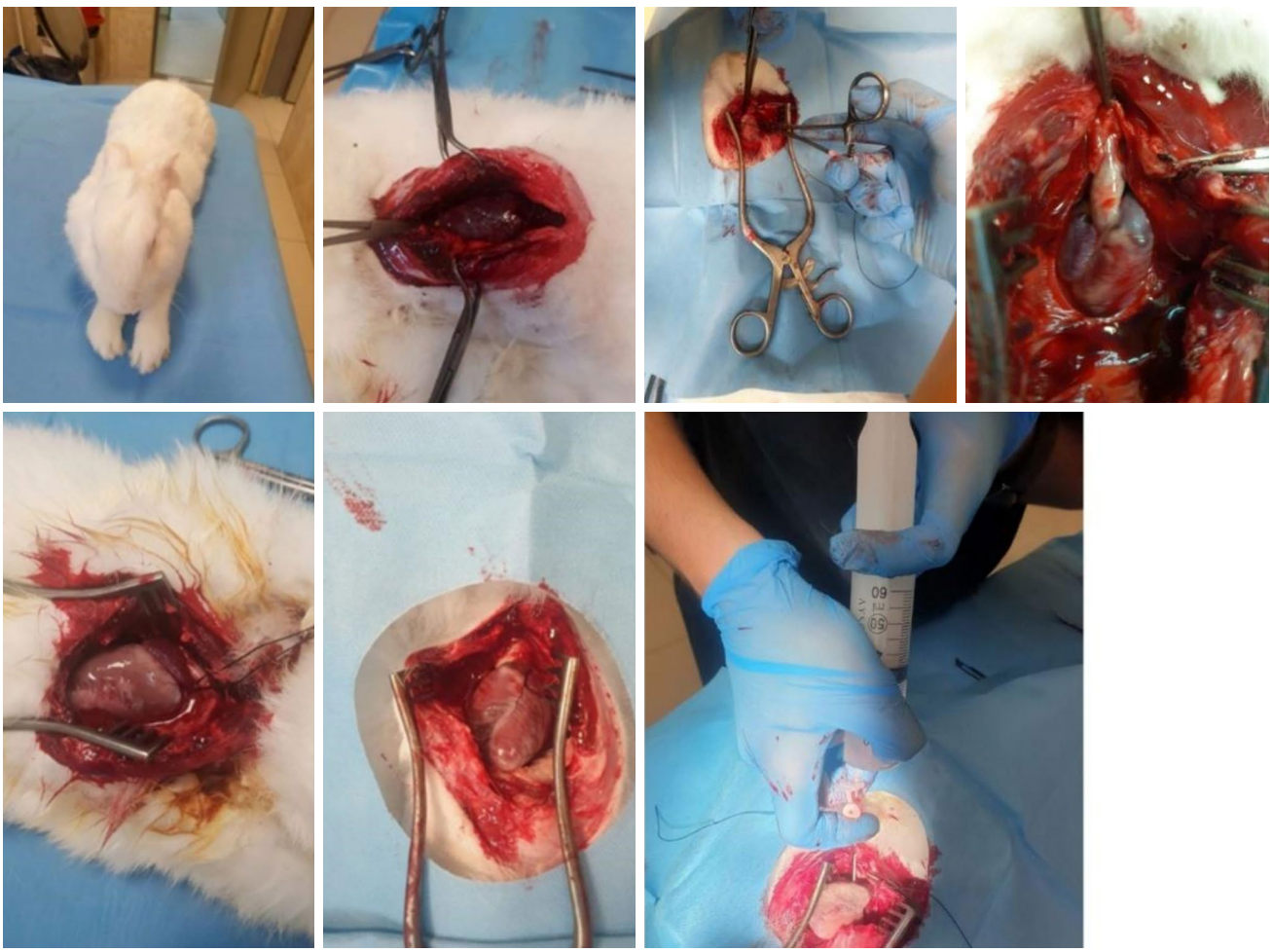

Figure 1. Sample collection from the experimental animals.

1-weighted, score 0-weighted, and score 2-weighted distributions at 30 min, respectively; there was a statistically significant difference between the groups (p<0.001). The St. Thomas, DN, and control groups showed score 1-weighted, score 0- and score 1-weighted, and score 2-weighted distributions at 60 min, respectively; there was a statistically significant difference between the groups (p=0.005). The St. Thomas, DN, and control groups showed score 2-weighted, score 1-weighted, and equal score 2- and score 3-weighted distribution at 90 min, respectively; there was a statistically significant difference between the groups (p=0.009, Table 1). Figure 2 displays time-related score changes according to H&E staining.

When the scoring of caspase 3 staining according to time was examined, it was observed that the St. Thomas, DN, and control groups showed equal score 1-and score 2-weighted, score 1-weighted, and score 3-weighted distributions at 30 min, respectively; there was a statistically significant difference between the groups (p=0.001). The St. Thomas, DN, and control groups showed score 3-weighted, equal score 2-and score 3-weighted, and score 3-weighted distributions at 60 min, respectively; there was a statistically significant difference between the groups (p<0.001). The St. Thomas, DN, and control groups showed score 3-weighted, score 2-weighted, and score 3-weighted distributions at 90 min, respectively; there was a statistically significant difference between the groups (p=0.010, Table 2). Figure 3 demonstrates time-related score changes according to caspase 3 staining.

When the scoring of Cx43 staining according to time was examined, it was observed that the

Table 1
Scoring of H&E staining by time

	St. Thomas	Del Nido	Control	*p*
30th min.				
Score 0	1	6	0	<0.001
Score 1	5	0	1	
Score 2	0	0	5	
Score 3	0	0	0	
60th min.				
Score 0	0	3	0	0.005
Score 1	3	3	1	
Score 2	3	0	4	
Score 3	0	0	0	
90th min.				
Score 0	0	1	0	0.009
Score 1	1	4	0	
Score 2	3	1	3	
Score 3	2	0	3	

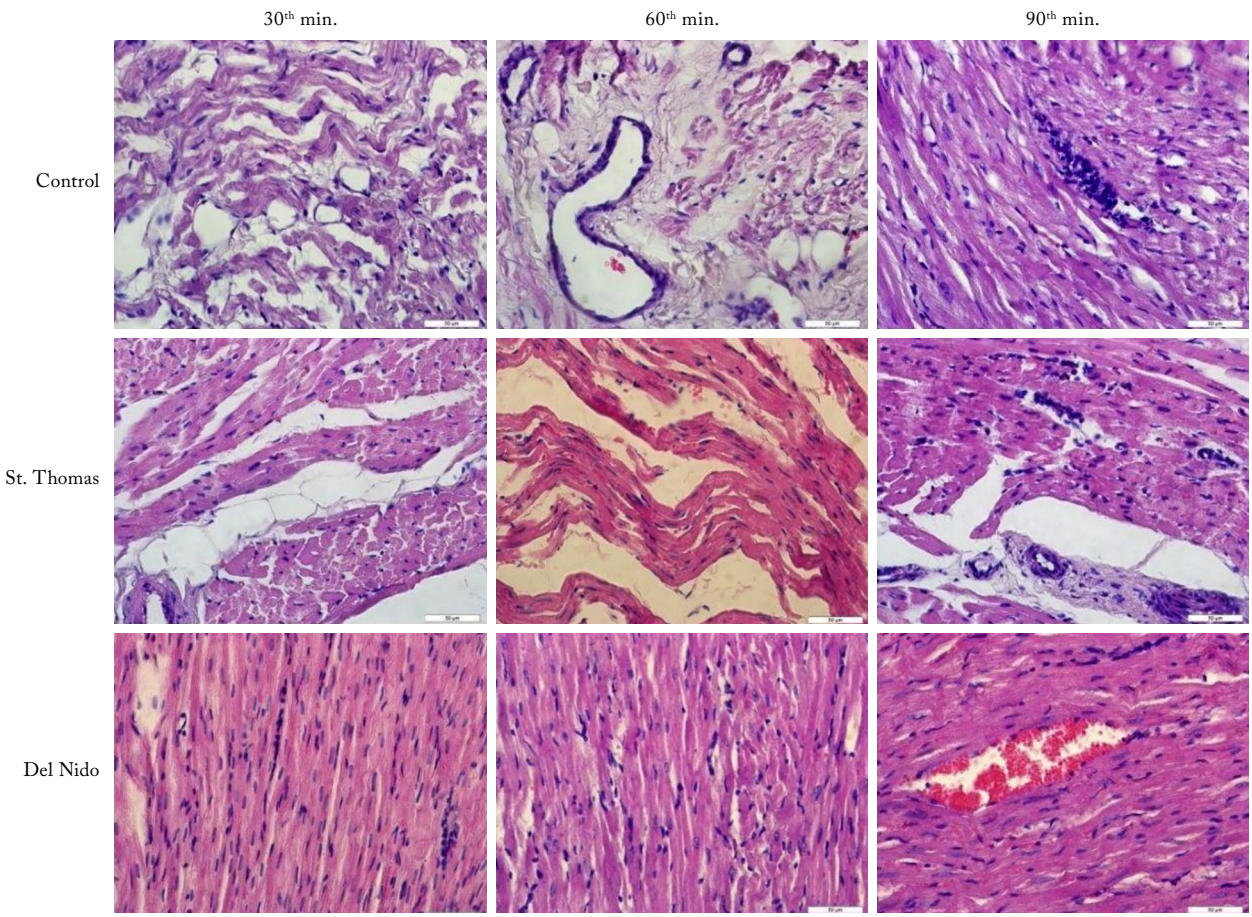

Figure 2. Time-related score changes according to H&E staining (50 μm).

Table 2
Scoring of caspase 3 staining by time

	St. Thomas	Del Nido	Control	*p*
30th min.				
Score 1	3	4	0	
Score 2	3	2	0	0.001
Score 3	0	0	6	
60th min.				
Score 1	0	3	0	
Score 2	2	3	0	<0.001
Score 3	4	0	6	
90th min.				
Score 1	0	1	0	
Score 2	2	5	0	0.010
Score 3	4	0	6	

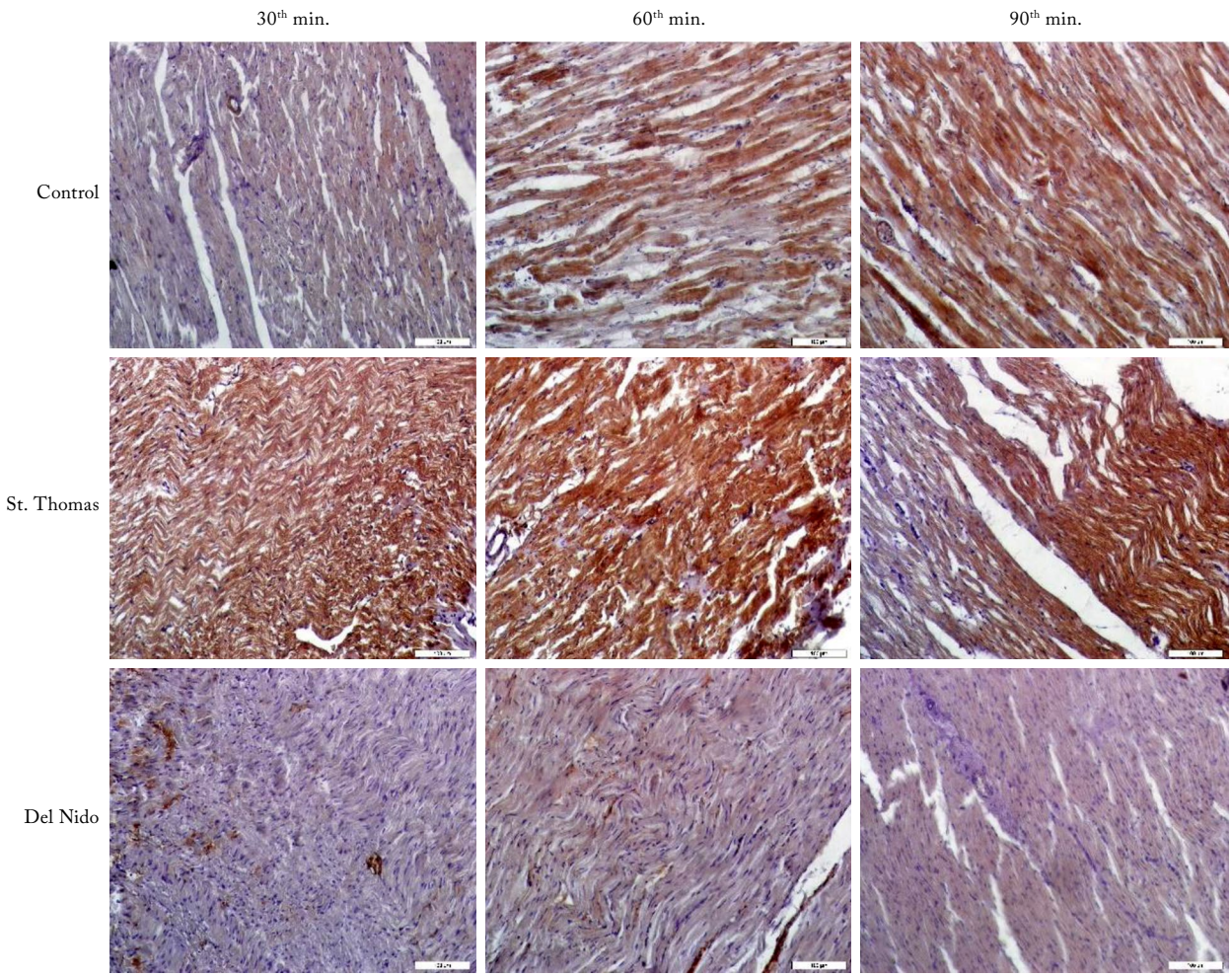

Figure 3. Time-related score changes according to caspase 3 staining.

Table 3
Scoring of C×43 staining by time

	St. Thomas	Del Nido	Control	*p*
30th min.				
Score 1	2	5	0	
Score 2	4	1	6	0.024
Score 3	0	0	0	
60th min.				
Score 1	1	1	0	
Score 2	4	5	2	0.033
Score 3	1	0	4	
90th min.				
Score 1	0	0	0	
Score 2	1	2	0	0.144
Score 3	5	4	6	

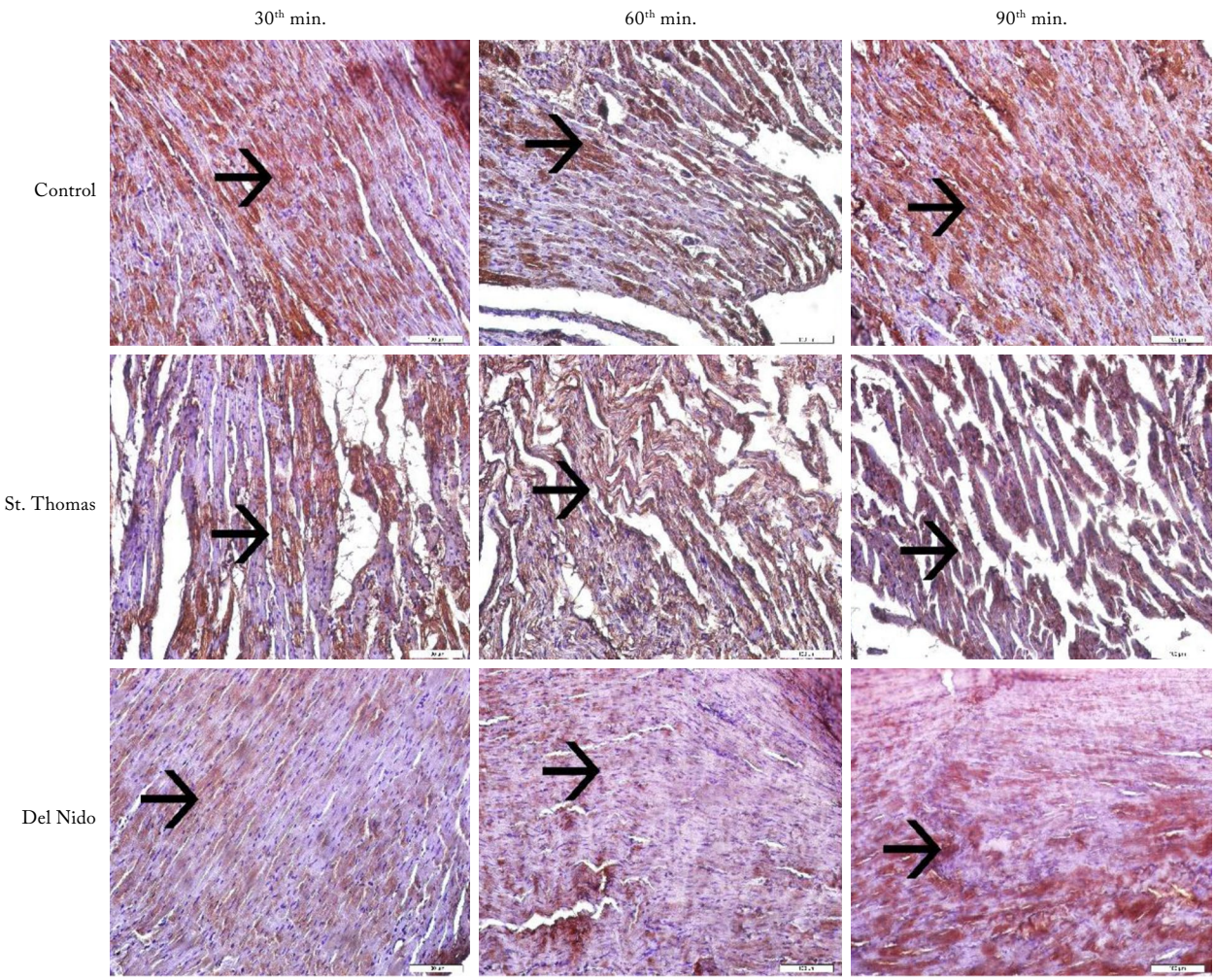

Figure 4. Time-related score changes according to C×43 staining.

St. Thomas, DN, and control groups showed score 2-weighted, score 1-weighted, and score 2-weighted distributions at 30 min, respectively; there was a statistically significant difference between the groups (p=0.024). The St. Thomas, DN, and control groups showed score 2-weighted, score 2-weighted, and score 3-weighted distributions at 60 min, respectively; there was a statistically significant difference between the groups (p=0.033). The St. Thomas, DN, and control groups showed equal score 2-and score 3-weighted, score 3-weighted, and score 3-weighted distributions at 30 min, respectively; there was no statistically significant difference between the groups (p=0.144, Table 3). Figure 4 exhibits time-related score changes according to Cx43 staining.

DISCUSSION

In this study, the cardioprotective effects of St. Thomas and DN cardioplegia, two different cardioplegia solutions used in cardiac surgery, were compared by a histological examination performed on tissues taken from rabbits to observe cellular damage. The DN cardioplegia solution, often used with blood in the research of cardioplegia solutions, was developed in the 1980s to obtain an effective single dose cardioplegia in pediatric cardiac surgery.[1,5] The effect of DN cardioplegia, which has recently been used in adult surgery, on cellular processes has not been experimentally determined.[1,5] In this study, we evaluated St. Thomas and DN cardioplegia on a cellular basis with caspase 3, Cx43, and H&E staining, which measures the pH value change due to infiltration in the cell cytoplasm, and evaluated their cellular protection and tissue damage in cardiac surgery in a 90-min period.

Enzymes in the extracellular matrix are activated by oxidative mediators and participate in cell damage processes. Therefore, it is important to evaluate these processes for the tissue to be transplanted.[6,7] In this study, scoring was made semiquantitatively based on the prevalence (0: 0-25%; 1: 26-50%; 2: 51-75%; 3: 76-100%) and severity (0: none; 1: mild; 2: moderate; 3: severe) of staining immunoreactivity. The total staining score was obtained by calculating the severity in prevalence.[8]

In a study using DN cardioplegia, both mitochondrial damage and foreign cell formation were evaluated using H&E staining in tissues after ischemia/reperfusion, and it was reported that cold ischemia can be safely performed using DN cardioplegia.[9] According to the analysis of H&E staining in our study, bacterial, parasitic, or fungal tissue formation in the tissues treated with cardioplegia was more prominent in the control group, while it was at a very low level in the DN group. In addition to intracellular protection, the protection of the St. Thomas group was at an acceptable level in the formation of extracellular bacteria, parasites, or fungal tissue.

Caspase immunoreactivity observed in the cardiomyocyte cytoplasm was observed to be intense in the control group. On the other hand, DN application was found to decrease caspase 3 immunoreactivity in cardiomyocytes. In the St. Thomas group, although caspase 3 immunoreactivity in cardiomyocytes was significantly lower than in the control group, it was quite intense compared to DN application. In the examination of caspase 3 activity, we found that the cardioplegia used in both groups was protective on a cellular basis compared to the control group, but the best protection was achieved with the DN group. According to the evaluation criteria of caspase 3, we believe that the protective feature between cardioplegia may be more prominent in longer measurements. However, our results in this study were similar to those in the literature.[10-12]

In our study, when the heart tissue at 30 min in the DN group was evaluated, it was found that the structure of the cells was preserved, and the muscle fibers had a normal appearance. Although local lymphocyte infiltration was observed, the cardiac muscle appeared normal when all groups were evaluated. In the heart tissue at 60 min, leukocyte infiltration was observed around the vessel in places, and although some areas appeared edematous, the myocardium preserved its normal histological appearance. In the 90th min, leukocyte infiltration around the vessel in the myocardial tissue, areas of hemorrhage, albeit very rarely, and areas with necrosis were observed in the DN group. Interstitial edema and local eosinophilic changes have been detected in some rabbits. In our study, caspase 3 and Cx43 half-life and the possibility of ischemia started to become evident at 60 min, and our results were longer than the reported half-life in previously published studies with adult patients.[13,14]

Ota et al.[15] have found a single dose of cardioplegia was administered to 70% of the patients in the

DN group, and the rates reported in adult studies conducted in different centers[16] range from 40 to 84%. Less frequent dosing ensures uninterrupted surgeon operation and reduces the risk of contamination. These advantages of DN may facilitate myocardial protection during adult cardiac surgery.

In this study, it was observed that serum and tissue caspase 3 activities increased in ischemic tissue in the 90th min following myocardial reperfusion injury as an indicator of increased apoptosis. However, we believe that this protection is likely to decrease in cases where the reperfusion time is longer.

The limitation of the study was that the hearts of the rabbits could not be reperfused since there was no tube set for the rabbits.

In conclusion, the most adverse tissue damage observed were localized hemorrhage and localized necrosis areas at the end of 90 min of cellular damage. Both cardioplegia applications significantly reduced tissue loss compared to the control group. Nonetheless, we believe that DN cardioplegia has a longer application time and better protection, and our study supported that by showing histopathological markers. Hence, DN cardioplegia is a safe method for adult cardiac surgery.

Ethics Committee Approval: The study protocol was approved by the Pamukkale University Ethics Committee (date: 23.06.2022, no: PAUHDEK-2021/52). The study was conducted in the Pamukkale University Experimental Animals Laboratory in accordance with the relevant ethical principles of the Declaration of Helsinki.

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

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Cardiovascular Surgery and Interventions

Case Report Open Access

A rare case of left main coronary artery atresia misdiagnosed as an anomalous left coronary artery from the pulmonary artery and presented as dilated cardiomyopathy

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ABSTRACT

Left main coronary artery atresia is one of the rarest congenital anomalies characterized by the absence of the left coronary ostium and the left main trunk. This case report presents an extremely rare left main coronary artery atresia case in a 14-week-old female infant presenting with severe symptoms of dilated cardiomyopathy. The patient underwent surgery after successful weaning from extracorporeal membrane oxygenation (ECMO) support but died because of cranial complications after the second run of ECMO.

Keywords: Bland-White-Garland syndrome, cardiac surgery, congenital heart disease, extracorporeal membrane oxygenation, left main coronary artery disease.

Coronary artery anomalies are relatively uncommon congenital disorders of the coronary artery anatomy. The incidence of coronary artery anomalies has been reported to be 0.6-1.3%.[1] Left main coronary artery (LMCA) atresia (LMCAA) is the rarest form of congenital coronary malformations, in which the coronary ostium and the main trunk in the left coronary artery (LCA) system are absent.[2] Thus, blood flows through collateral vessels from the right coronary artery (RCA) to the LCA.[3] Clinical presentation, management, and prognosis of this disease depend on the characteristics of the collaterals and native vessels.[4] Herein, we report a case of congenital LMCAA, misdiagnosed as an anomalous LCA from the pulmonary artery (ALCAPA).

CASE REPORT

A 14-week-old and 7 kg female infant, who had respiratory distress worsened after bronchiolitis, was admitted to another hospital. According to the echocardiographic examination in this center, the left atrium and left ventricle were greatly enlarged and left ventricular contractions were markedly decreased (shortening fraction: 13%), indicating dilated cardiomyopathy. A moderate degree of regurgitation was observed in the mitral and tricuspid valves. Pulmonary arterial pressure was measured to be approximately 60 mmHg through the tricuspid valve regurgitation. Since the patient had cardiogenic shock, intravenous immunoglobulin, hydrocortisone, and inotropic support drugs were started with the preliminary diagnosis of myocarditis. The patient was placed on venoarterial extracorporeal membrane oxygenation (ECMO) due to the low cardiac output leading to multiorgan failure using neck vessels. After 10 days of ECMO support, the patient was successfully weaned and separated from ECMO support. After three days of ECMO decannulation, both coronary multidetector computed tomography (MDCT) and cardiac catheterization was performed with a suspicion of ALCAPA syndrome. Figure 1 represents the right ventricle stuck between the sternum and the left ventricle. A hugely dilated left atrium and the left ventricle can be seen in Figure 2. Furthermore, Figure 2 shows the RCA and the absence of the left coronary ostium. The video of catheterization shows the retrograde flow of the LCA (Video 1). The patient was referred to our hospital for corrective surgery.

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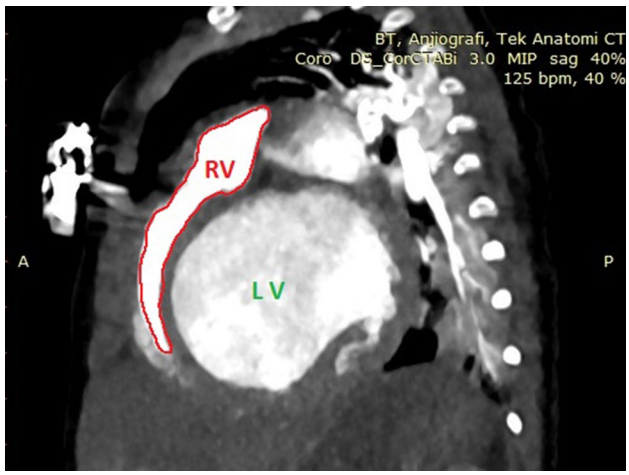


Figure 1. The right ventricle stuck between the sternum and the left ventricle.

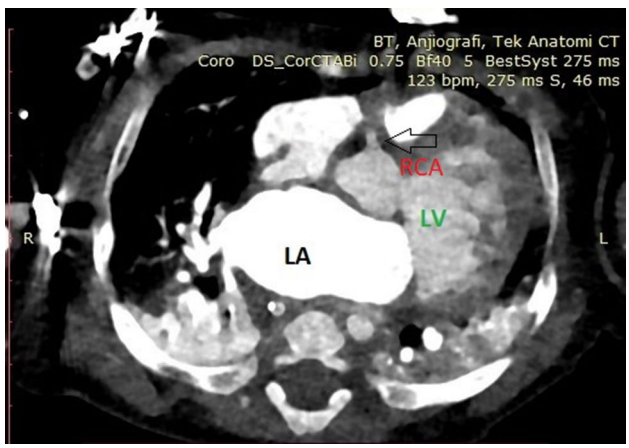
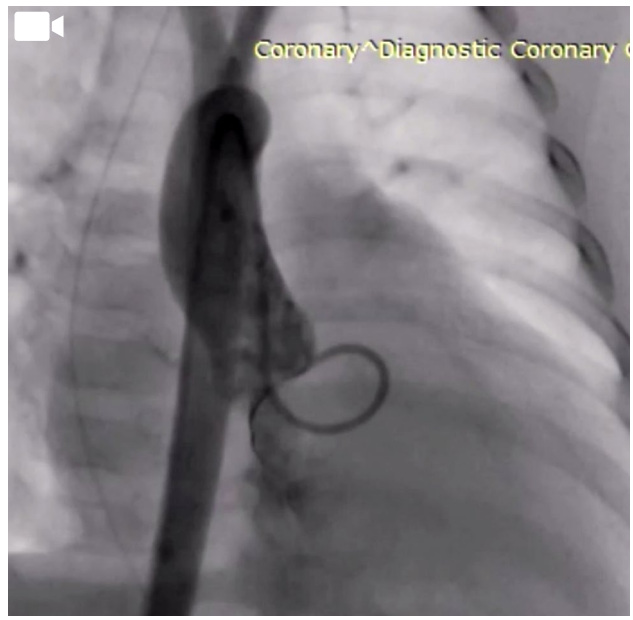


Figure 2. Hugely dilated left atrium and the left ventricle, the right coronary artery, and the absence of the left coronary ostium.

The patient had small ischemic lesions on the left frontoparietal, left thalamus, and basal ganglia on a computed tomography scan, which was evaluated by a pediatric neurologist. The patient underwent surgery under anticonvulsant treatment according to the recommendations of the pediatric neurologist. The patient could be referred for left ventricular assist device implantation or the transplantation list because of dilated cardiomyopathy. However, the patient was not in a position to wait long on the transplantation list. In addition, the need for lifelong anticoagulation treatment under ventricular assist device support could increase the risk of cerebral events. Therefore, we preferred surgical correction.



Video 1. The retrograde flow of the left coronary artery.

Although the origin of the LCA from the aorta or retrograde blood flow from the left anterior descending artery (LAD) to the pulmonary artery could not be visualized, the patient underwent an operation for LCA revascularization, with the possible preoperative diagnosis of ALCAPA. After a midline sternotomy and heparinization, aortic and bicaval cannulation was performed to initiate cardiopulmonary bypass. Diastolic cardiac arrest was provided with 30°C systemic hypothermia and antegrade tepid blood cardioplegia after cross-clamping. Tepid blood cardioplegia was repeated every 20 min until releasing the cross-clamp. The left side of the heart was vented via the patent foramen ovale. Pulmonary arteriotomy and aortotomy were performed. There were no left coronary ostia in the pulmonary artery or in the aorta.

The circumflex artery and LAD were visible but small in diameter. They had merged into a small blind pouch 2 cm away from the left coronary sinus of the aorta. There was no possibility for preparation and anastomosis to the aorta due to the tiny diameter and fragile vessel. The left internal mammary artery (LIMA) was harvested. The LIMA was not spastic, and its flow was sufficient. The LAD, which is located posterior to the pulmonary artery, just distal to the atretic ostium of LMCA, was opened, and a LIMA-LAD anastomosis was performed with 8-0 prolene. Pulmonary artery and aortotomy were

closed. The cross-clamp was removed after deairing. The patient was weaned from cardiopulmonary bypass with moderate inotropic support doses, including adrenaline, noradrenaline, and milrinone. The sternum was left open due to hemodynamic instability. Cardiopulmonary bypass time was 141 min, and cross-clamp time was 101 min.

According to the echocardiographic examination on the first postoperative day, the left ventricular shortening fraction was 15%, and there was a moderate degree of mitral regurgitation. The patient needed ECMO support due to the low cardiac output on the second postoperative day. The patient died of a massive cranial hemorrhage under ECMO support, documented with both head ultrasonography and a computed tomography scan, despite improving ventricular function (last measurement of shortening fraction: 20%) on the 10th postoperative day.

DISCUSSION

Left main coronary artery atresia is a rare condition with unclear etiology. In LMCAA, the left coronary system receives blood only from collateral arteries from the RCA. Thus, the heart may eventually be unable to cope with collateral circulations and develop myocardial ischemia. Patients mostly present with nonspecific symptoms depending on their age group and the formation of collateral vessels from the RCA to the LCA. Adult patients usually present with angina pectoris at an advanced age when collateral flow cannot keep pace with myocardial demands. Children and adolescents often present with chest pain, dyspnea, syncope, tachyarrhythmia, and sudden cardiac death.[2,3] Infants mostly present with growth retardation and myocardial infarction.[2] Catastrophic situations like sudden cardiac arrest, low cardiac output, and cardiomyopathy, as seen in our case, can also be the first symptoms of infants with LMCAA.[5,6] Since these symptoms are not specific to LMCAA, the clinical diagnosis might be neglected. Thus, other coronary anomalies should be excluded to reach a correct diagnosis. As stated in a retrospective study by Yildiz et al.,[1] LMCA was the most common anomalous vessel. Separate origins of LAD and circumflex artery from the left coronary sinus of Valsalva were the most common anomaly and should be excluded in patients presenting with symptoms of myocardial infarction. An ALCAPA is one situation that LMCAA can be confused with and should be differentiated from.[2,7]

Although congenital atresia of the LMCA usually occurs as an isolated cardiac lesion, concomitant anomalies including bicuspid aorta, supravalvular aortic stenosis, right coronary ostial stenosis, pulmonary stenosis, ventricular septal defect, and mitral valve prolapsus secondary to myocardial ischemia can be encountered.[4,8,9]

The diagnosis of LMCAA can be done by coronary angiographic findings, which usually show no left coronary ostium and LCA filled in a retrograde manner via the RCA instead of antegrade blood flow. In recent years, MDCT has also played an essential role in diagnosing LMCAA in older children and adults and can be used in patients suspected of congenital coronary artery abnormalities.[3,10] According to some researchers, MDCT provides more precise details in a less invasive way than coronary angiography and is thus recommended to evaluate congenital coronary abnormalities.[11] Multidetector computed tomography not only defines the anatomic course and the ostium shape but also has no complications as coronary spasm than conventional coronary angiography. However, there is no reliable research reporting the use of MDCT in infants with coronary anomalies.[9] The physician may merge findings that are revealed by transthoracic echocardiography examination and MDCT or cardiac catheterization. The absence of retrograde filling from LAD to the pulmonary artery may support the possible diagnosis of LMCAA.

The prognosis of LMCAA is poor.[2] Due to the symptomatic nature of LMCAA and the risk of sudden cardiac death, patients in the pediatric population with LMCAA should undergo surgical intervention to restore the antegrade flow to the left coronary system. Various surgical interventions have been described, and coronary artery bypass grafting using the internal mammary artery or the saphenous vein has been identified as the treatment of choice, regardless of the caliber of left-sided vessels.[4,8,12] A LIMA graft for LMCAA appears to be a reasonable early interventional approach with successful results one year postoperatively. Nevertheless, due to the rarity of this disease, long-term postoperative outcomes have not been reported.[2,4,5,8,9,11] Alternative to bypass grafting, direct surgical reimplantation or reconstruction of the LMCA using the azygos vein has been described to provide the shortest and most efficient way for blood to the myocardium.[6,12,13] The advantages of direct surgical reimplantation relative to bypass grafting is to provide antegrade

flow without a bypass material. However, direct surgical reimplantation could not be performed in small infants with LMCAA. The long-term results of bypass grafting in pediatric patients are reasonable and good results have been reported before.[12,14]

In conclusion, LMCAA is an extremely rare congenital coronary anomaly in which the left coronary ostium and the left main trunk in the LCA system are absent. Considering the severe symptoms, such as myocardial infarction or sudden cardiac death, surgical revascularization should most likely be the treatment choice.

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

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

Author Contributions: Idea/concept, writing the article: S.B., B.K., E.E.; Design, data collection and/or processing, analysis and/or interpretation, literature review, references and fundings; materials: S.B., B.K.; Control/supervision, critical review: E.E.

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Cardiovascular Surgery and Interventions

Case Report Open Access

Bilateral giant aneurysms of the carotid artery in one patient

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ABSTRACT

Extracranial carotid artery aneurysms are uncommon, life-threatening diseases typically resulting from atherosclerosis. In this case report, a 32-year-old male patient with a bilateral carotid artery aneurysm is presented. After the aneurysmectomy, Dacron graft interposition was applied to the right carotid artery. It was attempted to manage the complications that developed in the postoperative period. These patients require a more detailed and multidisciplinary approach, both intraoperatively and postoperatively.

Keywords: Aneurysms, carotid artery, giant.

Extracranial carotid artery aneurysms (CAA) are uncommon, life-threatening diseases typically resulting from atherosclerosis.[1,2] The incidence of peripheral artery aneurysms is 4%.[2] Although these aneurysms are typically asymptomatic, there is a high risk of cerebral embolism, nerve injury, and aneurysm rupture.[3]

Open surgery and endovascular treatments are the definitive treatment models. The prominence of open surgery in the treatment of carotid aneurysms reflects that the open surgery experience is considerable and endovascular treatment is in its developmental stages.[4] Standard surgical procedures involve end-to-end anastomosis and vein graft interposition.[4] In particular, aneurysms near the base of the skull make anastomosis hard, and their repair can damage nerves.[5] This shows how important endovascular therapy is with covered stents.[5] Herein, we present a patient with bilateral giant extracranial CAA successfully treated with open surgery.

CASE REPORT

A 32-year-old male presented to our clinic with pulsatile neck swelling on the right side (Figure 1). The patient had a history of a transient ischemic attack, slight mental retardation, psoriasis, and infertility but no prior trauma or neck surgery.

Computed tomography angiography revealed a right common CAA measuring 2.5 cm in width at the outflow level. More than 50% of the lumen in the distal segment of the common carotid artery (CCA) was stenotic. A 1.5-cm-wide aneurysm was found in the distal part of the left CCA (Figure 2).

The distance between the head and floor of the aneurysm permitted end-to-end anastomosis. It was decided to perform open surgery to reduce the

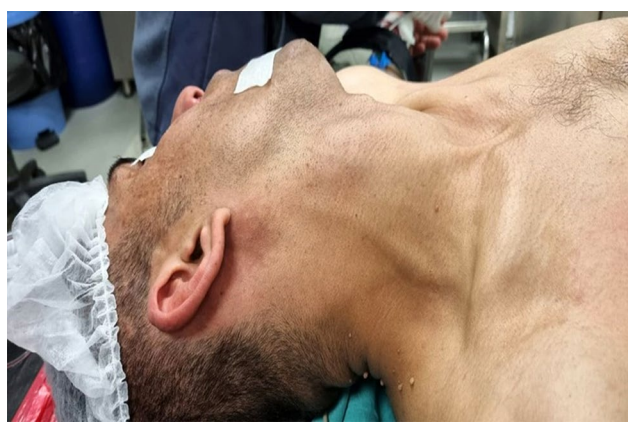

Figure 1. Giant mass on the right side of the neck.

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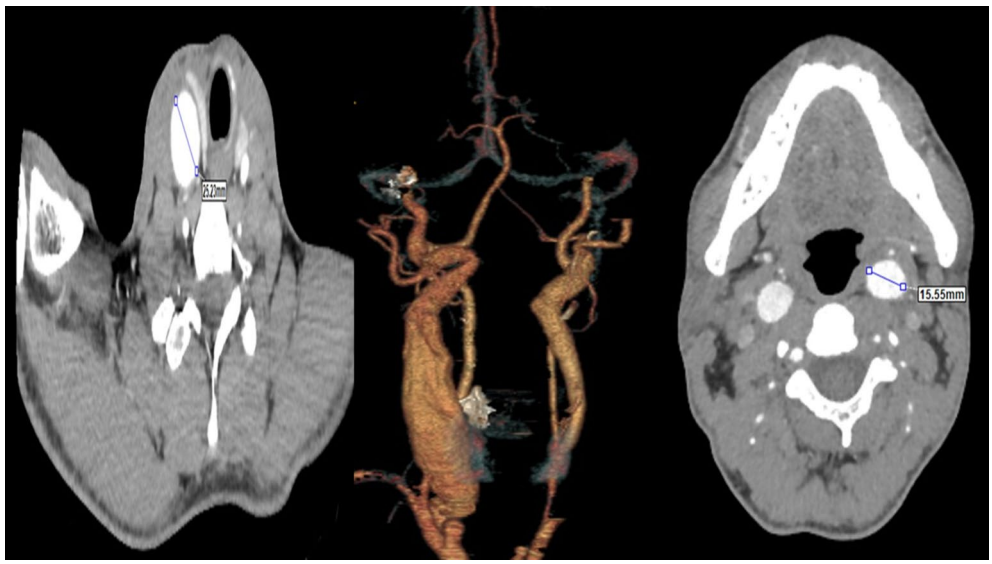

Figure 2. Aneurysm (2.5 cm) in the right CCA and aneurysm (1.5 cm) in the left CCA in computed tomography angiography.
CCA: Common carotid artery.

thrombus and the risk of a distal embolism, The shunt was not used because it was thought that cranial perfusion would be enough. During the surgery, cerebral oxygenation was monitored. The patient was draped following skin preparation under general anesthesia. The otolaryngology and plastic surgery departments explored the neck to prevent potential nerve damage and reduce tissue damage. An incision was made from the medial border of the sternocleidomastoid muscle. While protecting the cranial nerves, the aneurysm of the CCA was discovered. The aneurysm was removed after the CCA was clamped. Afterward, it was decided that both the proximal and distal parts of the CCA were long enough for anastomosis. The proximal and distal ends of the CCA were repaired with an end-to-end anastomosis using a 10-mm Dacron graft (Figure 3).

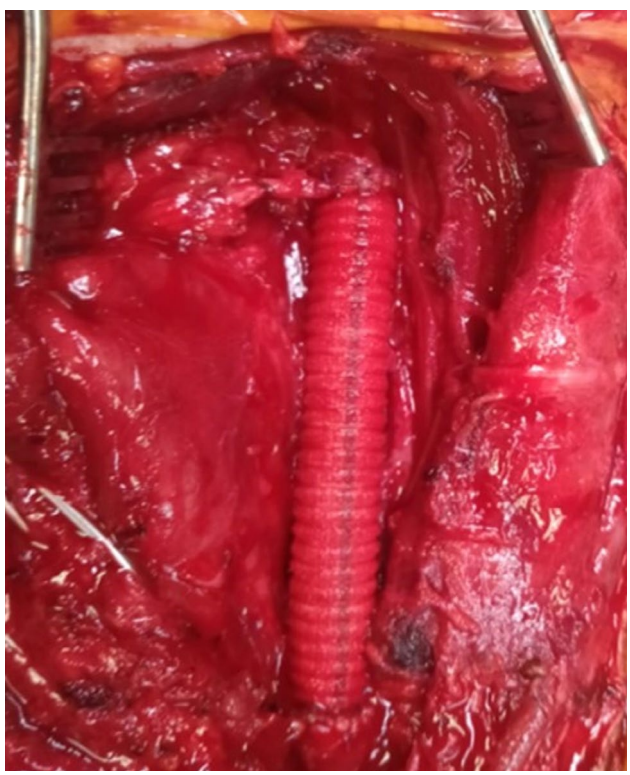

Figure 3. Final image of the Dacron graft (10 mm) after being placed.

The aneurysm wall sample was sent to the pathology department. The pathologic findings were consistent with an aneurysm, thrombus, and atherosclerosis (Figure 4). There were no fungi, spores, or hyphae.

After the operation, the patient's left upper and lower extremities did not have enough muscle tone. In the upper extremity, muscle strength was 1/5, whereas it was 2-3/5 in the lower extremity. In addition, facial paralysis was observed. Computed tomography angiography of the brain and carotid arteries showed localized embolic areas in the brain (Figure 5). On the recommendation of the neurology

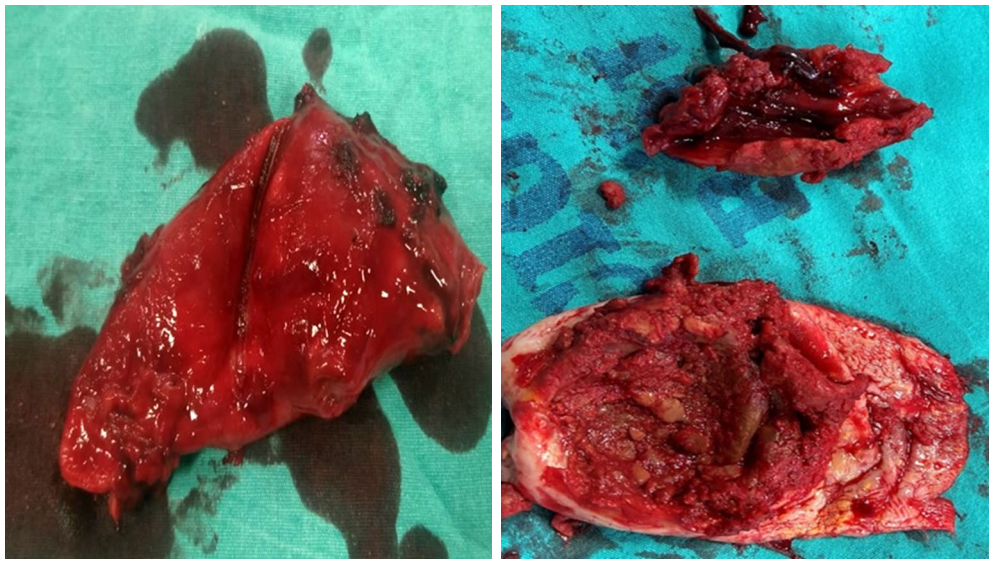

Figure 4. Excised aneurysm sac with thrombus fragments and atherosclerosis.

department, anticoagulant and mannitol medications were administered. Due to a hematoma, the patient was taken for revision, and the hematoma was removed on the second postoperative day. The rehabilitation program was implemented daily, and the patient's left-sided lack of mobility steadily improved. The patient's upper extremity muscular strength increased to 4/5, and the lower extremity muscular strength increased to 5/5. On the 14th postoperative day, the patient was released with an almost complete recovery of neurological deficits.

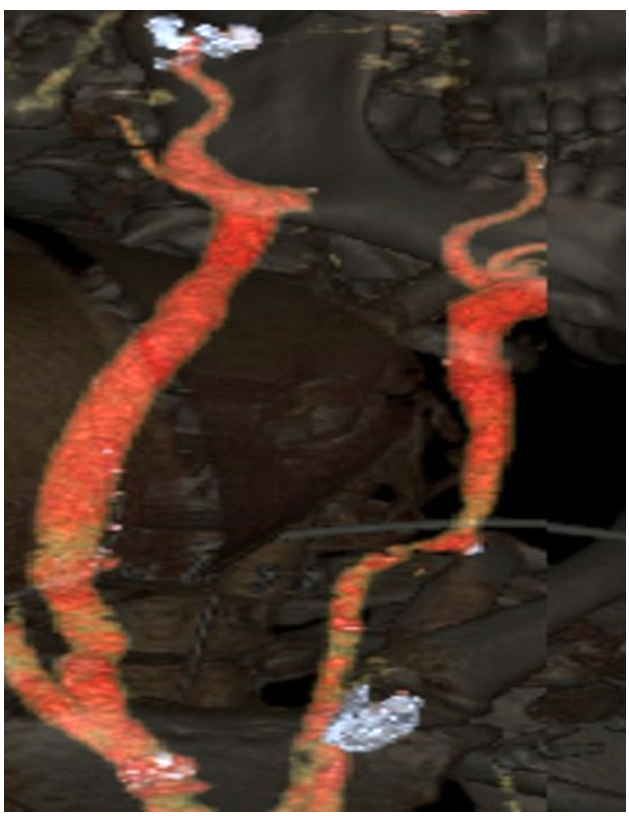

Figure 5. Three-dimensional carotid computed tomography angiography after the Dacron graft placement.

The left carotid artery was followed up for surgery after the patient was adequately rehabilitated. In the three- and six-month controls with the carotid computed tomography angiography, no progress was observed in the left carotid aneurysm.

DISCUSSION

The most common cause of extracranial CAA is atherosclerosis. Infrequently, connective tissue disorders, such as Marfan syndrome or Ehlers-Danlos syndrome, and infections, such as mycotic aneurysms, are also responsible.[6,7] Considering his age, our patient was young for atherosclerosis formation in the carotid artery and aneurysm formation in the bilateral common carotid arteries. A concomitant disease could not be identified, and the pathology report revealed no mycotic infections. Although a genetic test was not performed on the patient, the patient's medical history, physical examination, external appearance, and bilateral CAA suggested that a connective tissue disease (Ehlers-Danlos vascular type) might be the

cause of these aneurysms. The patient was referred to a genetic testing facility.

Excision of the aneurysm with open surgical repair is the first treatment option for carotid aneurysms. Depending on the size of the aneurysm, primary repair or graft interposition can be performed.[6-8] A less frequently used method in open surgery is carotid artery ligation. It may be done as a last resort when faced with a challenging situation due to its potentially fatal complications. A preoperative balloon occlusion test is indicated in patients with a high risk for carotid ligation.[3,4] The balloon occlusion test is a valuable screening test before carotid ligation, according to the study by Wong et al.[9] There may also be a thrombus burden in carotid aneurysms. This thrombus may result in a cerebrovascular event in patients like ours. Additionally, open surgical repair should be favored in these individuals.[6,7] The patient had a history of cerebrovascular disease, there was a thrombus in the aneurysm, and the aneurysm could not reach the base of the skull, requiring open surgical repair. The aneurysm required graft interposition for primary repair since it was too lengthy. Due to the large surface area covered by the aneurysm and the complexity of the examination, a multidisciplinary approach is necessary to avoid negative consequences. To preserve the nerves and muscles of our patient during surgery, we sought the aid of otolaryngology and plastic surgery specialists.

Huyzer et al.[10] described three patients with carotid aneurysms who underwent interposition grafts. One of these patients had a temporary paralysis of the facial nerve, and the other had a temporary paralysis of the vocal cord. After 14 months of follow-up, they discovered that all patients were alive and had no neurological deficits.

In a 15-year retrospective study, Fankhauser et al.[7] found 141 aneurysms and pseudoaneurysms. All 56% of the patients who received medical treatment did not experience aneurysm-related mortality or substantial morbidity. Asymptomatic patients were more likely to receive nonsurgical treatment (71%) than symptomatic patients (31%). This study demonstrates that some patients can be followed up with medical treatment, mainly if they are asymptomatic.

In conclusion, as extracranial CAA are associated with increased stroke incidence and mortality, they should be treated immediately. Open surgical repair should be the primary option. If the cerebrovascular event has not occurred and the patient's anatomy is acceptable, endovascular treatment may be considered for certain elderly patients with many comorbidities. Endovascular treatment will become increasingly prominent as technology advances in the following years. It should not be forgotten that asymptomatic patients and some selected patients can be managed with simple medicinal treatment. Choosing the treatment, determining the source of the aneurysm, and administering treatment for it can also prevent future complications.

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Cardiovascular Surgery and Interventions

Case Report Open Access

Pulmonary artery sling: A rare congenital anomaly masquerading as asthma in a one-year-old male patient

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ABSTRACT

Pulmonary artery sling is a rare congenital vascular anomaly that results in the abnormal development of the left pulmonary artery. This case report describes a one-year-old male patient with a history of respiratory issues who was initially treated for suspected infantile asthma. However, further investigation revealed a diagnosis of pulmonary artery sling, a rare congenital vascular anomaly that can cause airway and esophageal compression. The patient underwent surgical treatment to correct the abnormality. This case emphasizes the importance of considering pulmonary artery sling as a potential diagnosis in patients with respiratory symptoms and highlights the need for prompt diagnosis and treatment to prevent potential complications.

Keywords: Congenital vascular anomaly, pulmonary artery sling, respiratory symptoms.

Pulmonary artery (PA) sling is a rare congenital vascular anomaly that involves an incomplete formation of the sixth pair of aortic arcs during embryogenesis.[1] This results in the abnormal development of the left PA, which originates from the posterior wall of the right PA. The aberrant artery passes over the right main bronchus and in front of the trachea or carina and the esophagus before reaching the left lung hilus.[2] This condition can compress the trachea or esophagus, leading to abnormal development of the tracheobronchial tree and airway obstruction.[3]

Respiratory symptoms, such as dyspnea, stridor, and wheezing, typically manifest in the first years of life, and the degree of airway deformation is inversely related to the child's age. Younger children are at higher risk of airway cartilage deformation.[1-5] If left untreated, tracheal stenosis associated with PA sling can increase the risk of mortality. In this case report, we present a patient who was initially diagnosed with asthma but was later diagnosed with PA sling and underwent surgical treatment.[6]

CASE REPORT

A one-year-old male patient who had a history of frequent hospitalizations due to reactive airway disease and recurring lower respiratory tract infections since the patient was 40 days old presented to our hospital's emergency unit with complaints of cough and fever. On physical examination, we detected prolonged expiration, wheezing, inspiratory difficulty, and stridor. A chest X-ray showed pericardiac infiltration, and the patient was diagnosed with a lower respiratory tract infection. A 15-day course of antibiotic therapy and inhaler drugs was initiated, but the patient continued to experience coughing and inspiratory stridor, and thorax computed tomography revealed bilateral air confinement in the posterobasal region. Suspecting infantile asthma, inhaler treatment was continued, and the patient was discharged on the 15th day.

However, the patient returned to the hospital after a week with a recurring cough, and bronchoscopy revealed a narrowing in the posterior lateral wall at the entrance of the right main bronchus due to compression. Further thorax computed tomography angiography showed that the left PA originated from

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the right PA and wrapped around the right arch of the carina, creating pressure on the airway and esophagus (Figure 1). The patient was diagnosed with PA sling and recommended surgical treatment.

During the procedure, the patient was closely monitored with an electrocardiogram, blood oxygen saturation, invasive blood pressure, Bispectral Index (Medtronic, Minneapolis, MN, USA), and near-infrared spectroscopy (INVOS; Medtronic, Minneapolis, MN, USA). The blood pressure was 106/68 mmHg, the heart rate was 135/min, and the peripheral oxygen saturation was 98%. Midazolam was intravenously administered, and anesthesia was induced with sevoflurane inhalation. Intravenous fentanyl and rocuronium were administered, and the patient was intubated. We also performed central venous catheterization.

After the median sternotomy, we partially removed the thymus and opened the pericardium. We observed that the aberrant left PA originated perpendicular to the hilus at one-third of the right PA. As it emerged, it passed between the posterior of the trachea and the anterior of the esophagus and oriented towards the left hilus, creating an incomplete vascular sling. It was noted that it partially compressed the trachea and the right main bronchus. We released the aberrant left PA by dissection. Afterward, under normothermic cardiopulmonary bypass (CPB) and aortic cross-clamping, the left PA was transected from the right PA where it originated and passed through the trachea and esophagus to the left side. The left PA was anastomosed with the continuous technique end-to-side to its new place in the main PA (Figure 2). The patient successfully came out of CPB after 60 min without any complications.

The patient was transferred to the intensive care unit, where he remained intubated and sedated. The following day, the patient was extubated, and the patient was discharged on the sixth day after the procedure.

DISCUSSION

Pulmonary artery sling is a rare form of a vascular ring that accounts for only 1% of congenital cardiovascular anomalies.[1] Pulmonary artery sling can cause respiratory symptoms in children and is often misdiagnosed as asthma due to respiratory system-related findings.[1,3] It has been reported that early surgical intervention reduces postoperative respiratory complications.[6] Therefore, early diagnosis and appropriate surgical intervention are crucial for the management of PA sling. Due to varying

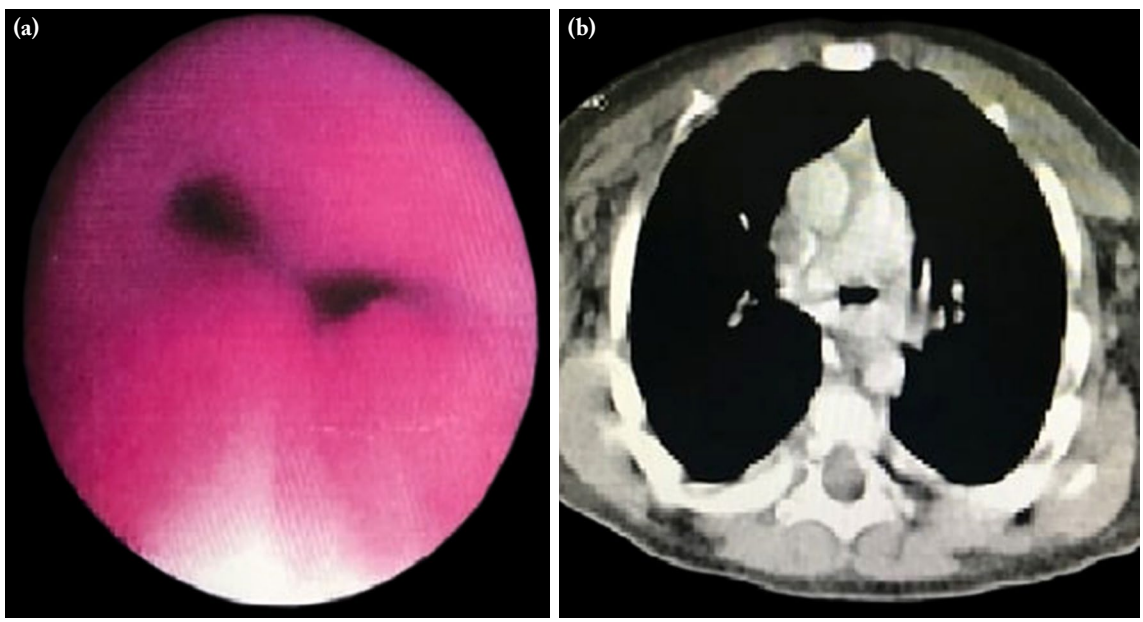

Figure 1. **(a)** Bronchoscopy image showing compression on the posterior lateral wall of the right main bronchus. **(b)** Computed tomography image showing pulmonary artery sling.

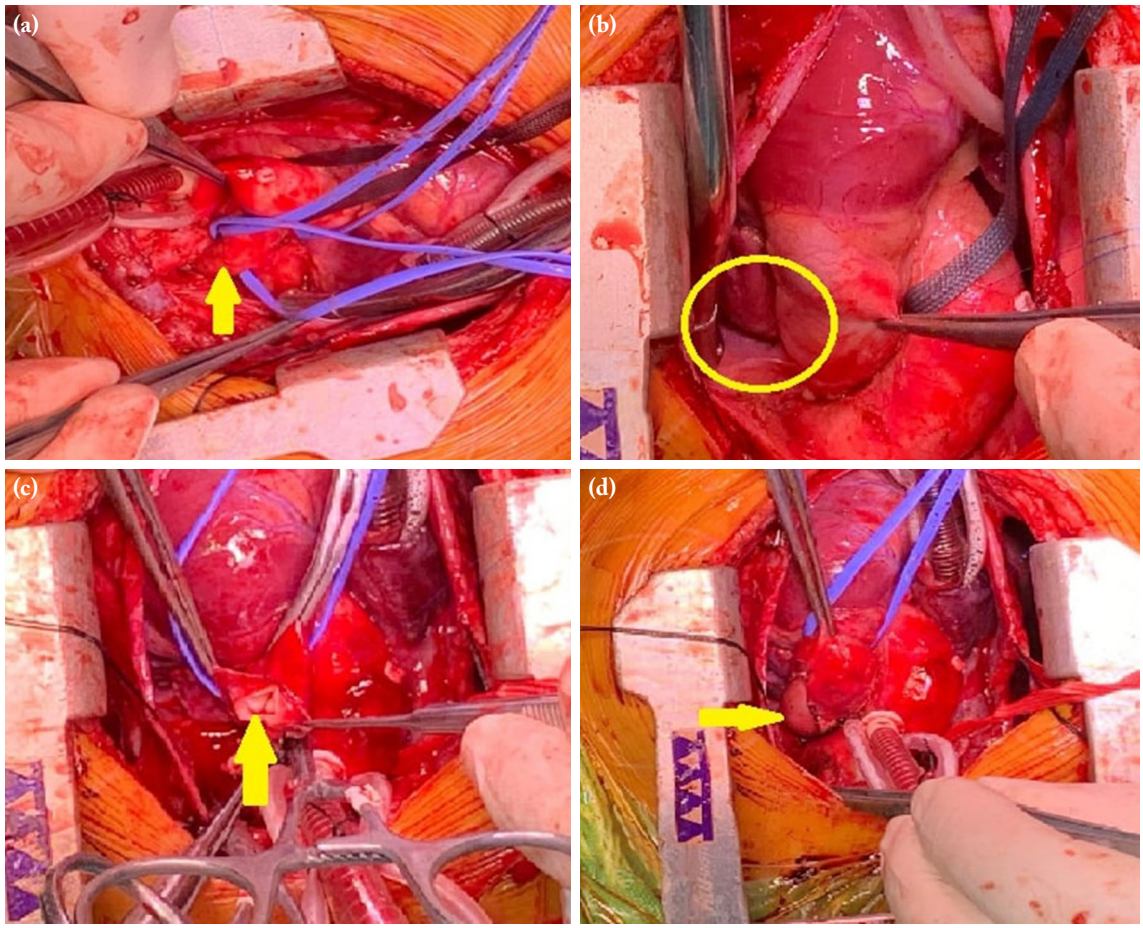

Figure 2. **(a)** View of the left PA originating from the right PA. **(b)** Absence of the left PA. **(c)** Anastomosis of the left PA to its anatomical position by separating it from the right PA. **(d)** Final view of the anastomosis of the left PA.

PA: Pulmonary artery.

degrees of respiratory distress in these children, airway management during surgery should be approached with caution. Vascular rings can act as anterior mediastinal masses during induction, leading to tracheal compression. It is recommended to use inhalation induction and to administer muscle relaxants only after ventilation is assured.[7]

Respiratory functions should be closely monitored since airway obstruction will continue after the operation.[3] Prolonged intubation, prolonged mechanical ventilation, and reintubations may be encountered in the postoperative period due to tracheomalacia. A study by Hong et al.[5] reported that postoperative early extubation, continuous positive airway pressure application, and early extubation might be useful to try again, even if reintubation was performed.

Early surgical intervention is recommended to prevent more severe complications that may arise as a result of long-term vascular compression of the airways.[6] In this type of vascular anomaly that requires surgical treatment, dissection at the point where the left PA originates and reimplantation to the main PA in front of the trachea are needed.[2] According to Backer et al.,[8] operations performed using median sternotomy and CPB allowed for the anastomosis of the left PA to the main PA in a safe and bloodless surgical area. The study found no complications associated with CPB, and reoperation was unnecessary.

In conclusion, when this extremely rare condition is diagnosed, early surgical intervention is necessary to prevent airway damage. Bronchoscopy should be performed to evaluate the airway condition before

surgery. Inhalation induction is recommended, and early extubation should be considered in the postoperative period.

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

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

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