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## RESEARCH ARTICLES



## CASE REPORTS



## VIDEO ARTICLE



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# Reviewers

# Reviewers

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Book: Baue AE, Geha AS, Hammond GL, Laks H, Naunheim KS. Gleen's thoracic and cardiovascular surgery. 1st ed. London: Appleton&Lange; 1991.

Book Chapter: Weinberg PM. Aortic arch anomalies. In: Allen HD, Clark EB, Gutgesell HP, Driscoll DJ (eds). Moss and Adams' heart disease in ınfants, children, and adolescents. 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 707-735.

Conference Paper: Davis L, Lee M, Sheridan B, et al. Berlin Heart EXCOR support in the first year of life. In: 32nd EACTS Annual Meeting; 18-20 October, 2018; Milan, Italy.

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### Correspondence

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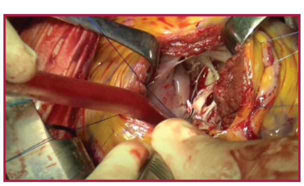
## Research Articles



## Case Reports





## VIDEO ARTICLE



## 2020 Index



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# Retrospective Evaluation of 85 Patients with Carotid Endarterectomy: Results of Different Techniques

**Cihan Yücel, Serkan Ketenciler, Melek Yılmaz, Nihan Kayalar**

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## Abstract

**Objectives:** Carotid endarterectomy (CEA) is a safe and effective surgical technique that prevents stroke in symptomatic and asymptomatic patients with severe internal carotid artery (ICA) stenosis. However, this surgical procedure is associated with a perioperative stroke risk of 2-7.5%. In this study, we examined the characteristics and early results of patients who underwent surgery for carotid artery stenosis in light of the current literature.

**Materials and Methods:** We retrospectively evaluated the data of patients who were diagnosed with symptomatic and asymptomatic ICA stenosis between January 2019 and January 2020 and underwent CEA in our hospital. A total of 85 patients were included in the study.

**Results:** The mean age of the patients was 67±8.2 years and 72.9% of the patients were male. The most common accompanying risk factors were smoking (64.7%) and hypertension (61.1%). Majority of patients had CEA for symptomatic carotid disease. One patient (1.1%) developed temporary hemiparesis. One patient (1.1%) developed transient ischemic attack. Six patients (7%) developed a postoperative hematoma and subsequently required revision. There was no mortality associated with the procedure.

**Conclusion:** Carotid artery surgery is a reliable method with low mortality and morbidity rates especially in those centers with high numbers and experienced surgical teams. A team approach including anesthetists, neurologists and interventional radiologists or interventional vascular surgeons is the key to critical decision making and the success.

**Keywords:** Carotid endarterectomy, near-infrared spectroscopy, carotid artery stenosis

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## Introduction

Atherosclerosis of the supra-aortic vessels, especially involvement of the bifurcation of the common carotid artery (CCA), is a significant cause of recurrent ischemic strokes. These make up 20% of all strokes, and the mortality rate ranges from 10% to 30%. Studies have found that the 5-year probability of developing ipsilateral stroke is 4% for patients with 50% asymptomatic carotid artery stenosis (ACAS) and 8% for patients with 70% ACAS[1].

Carotid endarterectomy (CEA) is a safe and effective surgical technique that prevents stroke in symptomatic and asymptomatic patients with severe internal carotid artery (ICA) stenosis[2]. The effectiveness of CEA in preventing stroke in patients with symptomatic carotid stenosis has been repeatedly confirmed in major clinical trials, but most significantly by the North American Symptomatic CEA Trial (NASCET) 1 and The European Carotid Surgery Trial[3]. However, this surgical procedure is associated with a perioperative stroke risk of 2-7.5%[4].

CEA is recommended in symptomatic patients with 70-90% carotid stenoses, provided documented procedural death/stroke rate is <%6[5].

In this study, we examined the characteristics and early results of patients who underwent surgery for carotid artery stenosis in light of the current literature.

## Materials and Methods

We retrospectively evaluated the data of patients who were diagnosed with symptomatic and asymptomatic ICA stenosis between January 2019 and January 2020 and underwent CEA in our hospital. A total of 85 patients were included in the study. The study was approved by the Ethics Committee of Training and Research Hospital (no: 48670771-514.10, date: 23/06/2020) and informed consents of patients were obtained. We included patients who underwent CEA alone and excluded those with concomitant coronary artery bypass grafting.

Patients with a carotid Doppler USG showing an ICA stenosis above 50-60% underwent computed tomography angiography of the carotid artery. One patient underwent digital subtraction angiography due to a high urea/creatine levels and was subsequently scheduled for CEA. Patients with symptomatic carotid artery stenosis of 70-99% and of 50-69% underwent carotid surgery as Class I and Class IIa indications whereas asymptomatic patients with carotid stenosis of 60-99% underwent surgery as Class IIa indication if they had suitable surgical anatomy and a life expectancy longer than 5 years[5]. In patients with bilateral lesions, the side of CEA was determined by the dominant hemisphere or the severity of the lesion as well as the side of symptoms if there were any.

Patients with bilateral ICA stenosis were followed strictly after the first operation but no patient had symptomatic disease.

All patients underwent a detailed preoperative cardiac evaluation. We recorded patients' neurological symptoms, comorbidities, smoking status, demographic characteristics, operative and postoperative data.

All patients were operated under general anesthesia when there were no contraindications. Invasive radial arterial pressure monitoring was performed along with standard monitorization. Cerebral oxygenation was monitored with near-infrared spectroscopy (NIRS) probes placed on the patients' frontal scalp. The results of NIRS were used to determine the need for carotid shunting. We incised the skin at the anteromedial side of the sternocleidomastoid muscle and explored and secured ICA, ECA and CCA with vascular tapes. Ten thousand units of systemic intravenous heparin were administered before the carotid arterial cross-clamp was placed with the aim of an ACT value above 200. The arteriotomy incision was started at the proximal site of carotid plaque and was extended distally to the ICA. The internal and external CEA was performed using the classic open endarterectomy technique. Arteriotomy was closed either primarily with 6-0 polypropylene sutures or by using saphenous or synthetic patch plasty technique in accordance to surgeon preference. The patients were extubated in the operating room or the intensive care unit depending on their hemodynamic and mental status. Patients were closely monitored in the postoperative intensive care unit for neurological problems. All patients were on dual antiplatelet therapy, 75 mg acetylsalicylic acid and clopidogrel postoperatively.

Statine treatment was administered in all patients and carotid Doppler ultrasound was performed at the postoperative 1st and 3rd month follow-ups.

## Results

A total of 85 patients who underwent CEA between January 2019 and January 2020 in our hospital were included in the study. The mean age of the patients was 67±8.2 years and 72.9% of the patients were male. The most common accompanying risk factors were smoking (64.7%) and hypertension (61.1%). The remaining demographic features and comorbidities are presented in Table 1.

Majority of patients had CEA for symptomatic carotid disease. There was a history of cerebrovascular event in 29 patients (34.1%) and a history of transient ischemic attack in 20 patients (23.5%) whereas 36 patients (42.4%) were asymptomatic. Bilateral ICA stenosis was present in 28 patients (32.9%). Twenty-four (28.2%) patients with transient ischemic attacks and minor ischemic strokes were operated between the 3rd to 7th days of the ischemic event in accordance with the 2017 European Society for Vascular Surgery Guidelines[5].

**Table 1.** Preoperative data of patients

| | | |
|---|---|---|
| **Age (years)** | 67±8.2 | 46-82 |
| **Ejection fraction** | 54.9±5.7 | 45-65 |
| **Variable** | **n** | **Total (%)** |
| **Sex** | | |
| Male | 62 | 72.9 |
| Female | 23 | 27.1 |
| **Hypertension** | 52 | 61.1 |
| **Smoking** | 55 | 64.7 |
| **Diabetes mellitus** | 48 | 56.4 |
| **Coronary artery disease** | 29 | 34.1 |
| **COPD** | 16 | 18.8 |
| **Symptom** | | |
| Stroke | 29 | 34.1 |
| TIA | 20 | 23.5 |
| Asymptomatic | 36 | 42.4 |
| **Bilateral lesion** | 28 | 32.9 |
| Right endarterectomy | 36 | 42.4 |
| Left endarterectomy | 49 | 57.6 |

*COPD: Chronic obstructive pulmonary disease, TIA: Transient ischemic attack, n: Number*

During the operation, we used NIRS parameters to monitor cerebral oxygenation. We observed that the regional cerebral oxygen saturation (rScO2) of five patients decreased by 25% below baseline, and subsequently placed a carotid shunt.

All patients underwent either right (42.4%) or left (57.6%) CEA. Operations were performed under general anesthesia in all except for two patients with contraindications. Primary closure of the arteriotomy was preferred in most patients (87.7%). In 28 patients with bilateral carotid disease, CEA was performed on the left side in 18 patients and on the right side in 10 patients.

Arteriotomy closure was done with saphenous vein patch in 19 cases. Two of these cases were re-explored for bleeding revision. Other complications occurred in cases that underwent primary closure.

One patient (1.1%) developed temporary hemiparesis. The symptoms resolved completely on the postoperative day 3. The subsequent brain diffusion MRI examination of the patient did not reveal any pathologies. One patient (1.1%) developed transient ischemic attack. Six patients (7%) developed a postoperative hematoma and subsequently required revision. There was no mortality associated with the procedure. The mean length of hospital stay was 3.4±1.2 days. All intraoperative and postoperative data are presented in Table 2.

## Discussion

Carotid artery stenosis is an important health issue due to high rates of complications such as stroke and subsequent mortality. Stroke is the third leading cause

Table 2. Operative and postoperative data of patients

| Variable | n | Total (%) |
|---|---|---|
| **Side of endarterectomy** | | |
| Right | 36 | 43.4 |
| Left | 49 | 57.6 |
| **Arteriotomy closure** | | |
| Primary | 66 | 87.7 |
| Patch | 19 | 12.3 |
| **Shunt use** | 5 | 5.5 |
| **Postoperative complications** | 0 | 0 |
| **Permanent cerebrovascular event** | | |
| Hemiparesis | 1 | 1.1 |
| TIA | 1 | 1.1 |
| Exploration for bleeding/hematoma | 6 | 7 |
| Mortality | 0 | 0 |
| **Variable** | **Mean ± SD (range)** | |
| **Clamp duration (minutes)** | 23±5.7 (9-35) | |
| **ICU stay (days)** | 1.14±0.44 (1-3) | |
| **Hospital stay (days)** | 3.48±1.2 (2-8) | |

*TIA: Transient ischemic attack, ICU: Intensive care unit, SD: Standard deviation, n: Number*

of death worldwide and 85% of strokes are ischemic[6]. Approximately 15-20% of ischemic strokes are caused by ICA disease[7].

Since first performed by De Bakey[8], CEA has been accepted as a safe and effective method for the treatment of carotid stenosis[9]. Recent studies recommend CEA to patients with symptomatic ICA stenosis ≥50% or asymptomatic ICA stenosis ≥60%, then following by medical treatment[10]. However, the stroke and mortality rate for CEA has been reported to be around 2-7.5%[4]. The Asymptomatic Carotid Artery Surgery Trial (ACST-1) has shown that although CEA has a 3% risk of stroke and death in asymptomatic patients, it significantly reduces the five-year risk of stroke compared to patients followed up with medical treatment. While none of our subjects died in this series of CEA, there was one case of hemiparesis (1.1%) and one with temporary ischemic attack (1.1%). These results are compatible to and are actually lower than the reported literature[11]. The main reason for this is the high number of carotid cases per year and vast experience of the team in our institution. Every case is discussed by the vascular team and appropriate approach, the side of endarterectomy and the possible need of shunt along with the proper anesthetic approach are determined by the team. Since our department is a part of a general hospital as opposed to being part of a cardiovascular hospital, we receive many patients from neurology department. Therefore, our pure carotid cases outnumber those cases with concomitant coronary bypass grafting surgery and to analyze a more homogenous group, concomitant cases were not included in the study.

Perioperative stroke, which occurs due to intraoperative embolism and hemodynamic impairment, reduces the benefit of surgery. Embolism usually occurs due to dissection, shunt placement and cross-clamping. Cerebral hypoperfusion during cross clamping may be a cause of perioperative stroke and therefore, its recognition is important, which largely depends on effective monitoring. The development of hypoperfusion may be prevented by inserting a carotid shunt. In our clinic, we do not routinely apply carotid artery shunting in operations. Since shunt placement carries a 1-3% risk of embolism or dissection[12], we use shunts only in certain cases. Our strategy to use shunting is when NIRS values drop by 20-25% from baseline or when the clamp time is anticipated to be long due to the anatomy of the patient and the carotid lesion. Although a detailed study is required to analyze effectiveness of NIRS monitorization to determine the need for carotid shunting, our low number of cerebrovascular complications suggest that this approach may actually have an important role during CEA and may help to avoid unnecessary shunting.

The timing of CEA is controversial. Early surgical intervention is becoming increasingly common in patients with transient ischemic attack or minor stroke. A large study consisting of 363 patients with stroke and unstable neurological deficits reported low mortality (1.6%) when the CEA was performed during the first week and high mortality (23.3%) when CEA was performed during the third week of the event[13]. Recent studies suggest that the operation should be performed shortly after the development of the cerebrovascular event, as further cerebrovascular events may occur while waiting for the operation[14]. In our clinic, we evaluate patients having cerebrovascular events together with the neurology department and schedule an operation as soon as possible according to the severity of the cerebrovascular event. We performed carotid surgery in 24 (28.2%) patients between the 3rd and 7th days from the onset of symptoms. These patients had minor stroke or transient ischemic attack with severe carotid stenosis. Strömberg et al.[15] reported a combined mortality and stroke rate as 3.6% for patients treated 3-7 days after qualifying event, which was lower than those treated on 0-2 days (11.5%) or after 14 days (5.4%). Our strategy in this group of patients is close in-hospital observation for a few days and performing surgery within a week from the onset of symptoms.

In recent years, endovascular interventions have become more common in the treatment of carotid artery stenosis and are currently preferred for high surgical risk patients. Therefore, more and more studies compare CEA and endovascular interventions in the treatment of carotid artery stenosis. However, although current studies show CEA as the gold standard for the treatment of carotid stenosis, more clinical studies are needed for a definitive conclusion. In our hospital, every case is discussed by multidisciplinary vascular team which includes an interventional radiologist and preferred intervention is determined. In patients with high surgical risk and suitable anatomy, endovascular intervention is preferred. In "Systolic and Pulse Pressure Hemodynamic Improvement by Restoring Elasticity" (SAPPHIRE) study, conditions related to high surgical risk were defined as congestive heart failure, severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, previous radical neck surgery, cervical radiation therapy, recurrent stenosis after CEA and age >80 years[16]. We follow a similar approach with a few differences. Since the carotid lesions in elderly carry a heavy calcific load, if patient does not have any other risk factors and is in good clinical condition, we prefer surgery in these patients as well. In addition, in patients with total occlusion of the contralateral carotid artery, we prefer surgery if early insertion of shunt is anticipated to be possible.

## Conclusion

Our clinical experience and early surgical results are consistent with the literature. Carotid artery surgery is a reliable method with low mortality and morbidity rates especially in those centers with high numbers and experienced surgical teams. A team approach including anesthetists, neurologists and interventional radiologists or interventional vascular surgeons is the key to critical decision making and the success.

### Ethics

**Ethics Committee Approval:** This study was approved by the Ethics Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital (no: 48670771-514.10, date: 23/06/2020).

**Informed Consent:** Informed consents of patients were obtained.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

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# Evaluation of the Relationship Between Platelet Indices and Mitral Restenosis After Percutaneous Mitral Balloon Valvuloplasty

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## Abstract

**Objectives:** Percutaneous mitral balloon valvuloplasty (PMBV) has been established as an effective and safe treatment modality for symptomatic patients with severe rheumatic mitral stenosis. Wilkin scores ≤8 are associated with higher rates of procedural success and lower rates of restenosis. It is well-known that platelets have a substantial role in thromboembolic complications of rheumatic mitral stenosis and various studies have showed that increases platelet (PLT) activity in rheumatic mitral stenosis. The aim of this study was to assess the usefulness of PLT indices as a predictor of restenosis in patients who underwent PMBV.

**Materials and Methods:** We retrospectively enrolled 178 consecutive patients who underwent PMBV. Patients were classified into two groups. The study group (n=21) included patients whom we performed redo PMBV during their follow-ups as a result of mitral restenosis following previous PMBV (index procedure) and the control group (n=157) included patients who did not undergo a redo PMBV. PLT indices including PLT count, Plateletcrit (PCT) and mean platelet volume (MPV) values were evaluated in these groups.

**Results:** In the study group, PLT count (210±49 vs 241±62, p=0.010), PCT [0.203 (0.173-0.230) vs 0.260 (0.243-0.290), p<0.001] and MPV [9.7 (8.7-11.1) vs 10.5 (9.8-12.0), p=0.021] values were significantly higher in the restenosis group when compared to the control group. Receiver operating characteristic analysis showed cut-off values for MPV crossed

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## Abstract

the curve at 9.65 (sensitivity 81.0% and specificity 49.7%) and for PCT crossed the curve at 0.241 (sensitivity 76.2% and specificity 87.9%).

**Conclusion:** PLT indices including PLT count, MPV and PCT might be feasible and easy parameters to predict possible restenosis after PMBV.

**Keywords:** Rheumatic mitral stenosis, platelet, platelecrit, percutaneous mitral balloon valvuloplasty

## Introduction

Percutaneous mitral balloon valvuloplasty (PMBV) is an effective and safe treatment modality for symptomatic patients with severe rheumatic mitral stenosis in clinical practice[1-3]. Studies in literature demonstrated that pre-procedural clinical and echocardiographic characteristics and post-procedural outcomes had strong association in between[4]. In current clinical practice, Wilkins score (WS) is used to determine the morphology of mitral valve in transthoracic echocardiography (TTE) and score includes leaflet thickening, calcification, mobility and subvalvular fusion[5,6]. WS ≤8 is associated with higher rate of procedural success and lower rate of restenosis[7]. Long-term adverse events after PMBV including mitral restenosis, occurrence of mitral regurgitation (MR), or progression of other valvular diseases were evaluated in previous studies. According to those studies, the incidence of restenosis was approximately 40% depending on the patient population, valve morphology, and duration of follow-up. In addition, major predictive factors with regard to being free from restenosis were WS ≤8 and post-procedural mitral valve area (MVA) ≥2.0 $cm^2$[8,9].

Platelets have substantial role in thromboembolic complications of rheumatic mitral stenosis. Evidence by *in vivo* hemostatic markers revealed that rheumatic mitral stenosis was associated with increased platelet (PLT) activity[10,11]. Increased PLT activity caused increased production of thromboxane A2 and beta thromboglobulin, which resulted in a pro-thrombotic state in this patient population[12]. PLT indices such as PLT count, mean platelet volume (MPV), and plateletcrit (PCT) are measured by automated blood cell analyzers and are reliable markers of PLT activity.

Therefore, in this study, we aimed to evaluate the usefulness of PLT indices as a predictor of restenosis and assessed long-term outcomes in patients who underwent PMBV.

## Materials and Methods

### Study Population

We retrospectively enrolled 178 consecutive patients presenting with symptomatic rheumatic mitral stenosis with favorable valve morphology, who underwent PMBV at our hospital between January 2010 and December 2019. Informed consent was obtained from all patients in accordance with a protocol approved by the local ethics committee (Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee, decision no: 2020/58, date: 18.08.2020). Patients with MR more than mild or evidence of left atrial (LA) thrombus by transesophageal echocardiography (TEE) were excluded from the study because those parameters were contraindications for PMBV. Patients with concomitant valve disease requiring surgical intervention and patients indicated for coronary artery bypass surgery were also excluded.

Then, patients were classified into two groups based on their follow-up findings. The study group was defined as patients whom we performed redo PMBV during their follow-up as a result of mitral restenosis following previous PMBV (index procedure) and the control group was defined as patients who did not undergo a redo PMBV. In the study group, restenosis was defined as a decrease in MVA >50% after the index PMBV together with MVA ≤1.5 $cm^2$ during follow-up. For each group, demographic characteristics, past medical records, laboratory values, procedural information, TTE and TEE parameters were noted. Echocardiographic evaluation included left ventricular ejection fraction (LVEF), MVA, systolic pulmonary artery pressure (sPAP), mean diastolic mitral gradient, WS, and LA diameter.

### Laboratory Measurements

Blood samples were drawn from the ante-cubital vein after a 12-hour fasting period and at most 24 hours before the procedure. PLT indices were measured in a blood sample collected in dipotassium EDTA tubes. An automatic blood counter (Sysmex, XT-2000i) was used for whole blood counts. PLT indices were measured within 30 minutes after sampling to prevent EDTA-induced PLT swelling. PCT, which defines the mass of PLT, is the volume occupied by PLT in the blood as a percentage. PCT was estimated according to the formula of PCT= PLT count ´ MPV/10.000[13,14].

### Echocardiographic Assessment

All patients underwent TTE examination using a GE Vingmed Vivid 5 echocardiography device (GE Vingmed Ultrasound, Horten, Norway) before the procedure. MVA and other conventional echocardiographic measurements in our center are routinely performed according to American Echocardiography Society criteria in daily practice[15]. Mitral valve apparatus morphology was evaluated by using WS which included semi-quantitative assessment of leaflet mobility and thickening, subvalvular changes, and valve calcification according to previous definitions[6]. In addition, all patients routinely undergo TEE examination in our center within 24 hours before the planned procedure in order to rule out left atrial or appendage thrombosis and assessment of mitral annular diameter and morphology of atrial septum. Pre-procedural echocardiographic parameters were noted for every patient.

### Procedural Technique

PMBV was performed via the trans venous (antegrade) approach through the femoral vein using a transseptal Brockenbrough needle as previously described[16]. Initial balloon size was selected according to body surface area. Maximum balloon size was determined by the following formula: [patient height (cm)/10+10][17]. All procedures were performed under TEE guidance. Procedure related mitral valve regurgitation was assessed by using echocardiography. According to our study, successful PMBV was defined as post-procedural MVA ≥1.5 $cm^2$ by Gorlin formula and post-procedural MR less than moderate by echocardiographic or angiographic evaluation immediately after PMBV.

### Statistical Analysis

Statistical analysis was made using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, New York, USA). Data were expressed as "n (%)" for categorical variables. The Pearson chi-square and Fisher exact tests were performed for categorical variables. After fitness to normal distribution was analyzed with the Kolmogorov-Smirnov test, data were expressed as "median ($25^{th}$ and $75^{th}$ percentiles)" for variables without a normal distribution and mean ± standard deviation for variables with normal distribution. While the Student-t test was used to compare quantitative variables with normal distribution, the Mann-Whitney U test was used to compare quantitative variables without a normal distribution. Receiver operating characteristic (ROC) analysis was conducted to determine the optimal PCT and MPV value to indicate mortality in terms of both sensitivity and specificity. The long-term restenosis curve for both MPV and PCT was analyzed using the Kaplan-Meier method, and statistical assessment was performed using the log-rank test. A p value <0.05 was considered to be statistically significant.

## Results

Baseline clinical and demographic characteristics of each group were provided in Table 1. There were no significant differences between two groups in terms of baseline clinical and demographic characteristics. On the other hand, the incidence of diabetes mellitus (DM) [7 (4.5%) vs 4 (19.0%), p=0.028] and the presence of atrial fibrillation (AF) [28 (17.8%) vs 12 (57.1%), p<0.001] were significantly higher in the study group compared to the control group. One hundred and fifty-seven patients without restenosis had PMBV between 27 and 84 months ago and restenosis was not detected during their follow up. Twenty-one patients with restenosis had previous PMBV between 36 and 60 months ago and had their redo PMBV in our hospital during their follow-up.

**Table 1.** Baseline demographic and clinical variables of study population

| | Restenosis (-) (n=157) | Restenosis (+) (n=21) | p value |
|---|---|---|---|
| Age (years) | 42±11 | 41±11 | 0.536 |
| Sex - female, n (%) | 127 (80.9) | 19 (90.5) | 0.227 |
| NYHA classification before PMBV | | | |
| NYHA I | 10 (6.4) | 2 (1.4) | 0.335 |
| NYHA II | 101 (64.3) | 11 (9.8) | |
| NYHA III | 42 (87.5) | 6 (12.5) | |
| NYHA IV | 4 (2.5) | 2 (9.5) | |
| Coronary artery disease (n, %) | 6 (3.8) | 1 (4.8) | 0.591 |
| Prior cerebrovascular event (n, %) | 6 (3.8) | 0 (0) | 0.465 |
| Diabetes mellitus (n, %) | 7 (4.5) | 4 (19.0) | **0.028** |
| Hypertension (n, %) | 16 (10.2) | 5 (23.8) | 0.080 |
| Peripheral embolic event (n, %) | 1 (0.6) | 1 (4.8) | 0.223 |
| Presence of atrial fibrillation (n, %) | 28 (17.8) | 12 (57.1) | **<0.001** |
| Follow-up period (months) | 60 (27 - 84) | 48 (36-60) | 0.377 |

*NYHA: New York Heart Association, PMBV: Percutaneous mitral balloon valvuloplasty, n: Number*
*Important p values are written in bold.*

In the study group, PLT (210±49 vs 241±62, p=0.010), PCT [0.203 (0.173-0.230) vs 0.260 (0.243-0.290), p<0.001] and MPV [9.7 (8.7-11.1) vs 10.5 (9.8-12.0), p=0.021] values were significantly higher when compared to the control group. Baseline laboratory values of both groups were shown in Table 2.

Although baseline MVA and echocardiographic parameters were similar in both groups, WS was significantly higher in the study group compared to the control group [8 (7-9) vs 9.5 (8-10), p=0.042]. Baseline TTE and TEE measurements were shown in Table 3.

Procedural and post-procedural data for the patients were shown in Table 4. The control group patients without restenosis included data for their PMBV. The study group patients who had restenosis included data for their redo PMBV. The successful PMBV was achieved in 17 (81.0 %) patients of the study group and 138 (87.9 %) patients of the control group. Comparison of outcomes of procedures and post-procedural TTE measurements were shown in Table 4. Procedural

**Table 2.** Laboratory parameters of patients with and without restenosis

| | Restenosis (-) (n=157) | Restenosis (+) (n=21) | p value |
|---|---|---|---|
| Creatinine (mg/dL) | 0.7 (0.6-0.81) | 0.7 (0.61-0.76) | 0.340 |
| Total cholesterol (mg/dL) | 177 (163-195) | 149(119-167) | 0.067 |
| LDL (mg/dL) | 105 (91-124) | 77 (58-93) | 0.057 |
| HDL (mg/dL) | 49±14 | 54±17 | 0.610 |
| Triglyceride (mg/dL) | 114 (71-145) | 84 (44-101) | 0.201 |
| Leukocyte ($10^3$/mL) | 7.32 (6.37-9.26) | 7.75 (6.84-8.26) | 0.558 |
| Platelet ($10^3$/mL) | 210±49 | 241±62 | **0.010** |
| Plateletcrit (%) | 0.203 (0.173-0.230) | 0.260 (0.243-0.290) | **<0.001** |
| Mean Platelet Volume (fL) | 9.7 (8.7-11.1) | 10.5 (9.8-12.0) | **0.021** |
| Hemoglobin (g/dL) | 12.73±1.84 | 12.44±1.54 | 0.495 |

*LDL: Low-density lipoprotein, HDL: High-density lipoprotein, n: Number*
*Important p values are written in bold.*

success rate and post-procedural TTE parameters except the mean gradient were similar between both groups. On the other hand, decrease in trans-mitral gradient was found to be significantly lower in the study group compared to the control group [5 (4-6) vs 6 (5-7), p=0.004].

ROC analysis was conducted to determine the optimal MPV and PCT cut-off values to indicate restenosis. The highest combined sensitivity and specificity values for MPV crossed the curve at 9.65 (sensitivity 81.0% and specificity 49.7%) (Table 5). The area under the curve (AUC) was 0.656 (95% CI: 0.541-0.770, p=0.021). The highest combined sensitivity and specificity values for PCT crossed the curve at 0.241 (sensitivity 76.2% and specificity 87.9%). The AUC was 0.826 (95% CI: 0.700-0.952, p<0.001) (Figure 1).

A Kaplan-Meier survival analysis also revealed that long term restenosis rate was found to be significantly higher in patients with higher PCT (Log-Rang p<0.001) and MPV (Log-Rang p<0.001) values (Figure 2 A, B).

**Table 3.** Pre-procedural transthoracic and transesophageal echocardiographic parameters of study groups prior to their first percutaneous mitral balloon valvuloplasty

| | Restenosis (-) (n=157) | Restenosis (+) (n=21) | p value |
|---|---|---|---|
| **Ejection fraction (%)** | 60 (60-65) | 65 (60-65) | 0.296 |
| **TTE** | | | |
| **sPAP (mmHg)** | 42 (35-55) | 45 (39-55) | 0.453 |
| **LA diameter (cm)** | 4.5 (4.2-4.8) | 4.7 (4.4-4.9) | 0.111 |
| **Wilkins score** | 8 (7-9) | 9.5 (8-10) | **0.042** |
| **Planimetric MVA (cm²)** | 1.1 (1.0-1.2) | 1.1 (1.0-1.3) | 0.417 |
| **MVA PHT (cm²)** | 1.1 (0.9-1.3) | 1.1 (1.0-1.2) | 0.739 |
| **Mean gradient (mmHg)** | 11 (9-14) | 11 (10-13) | 0.532 |
| **TEE** | | | |
| **sPAP (mmHg)** | 50 (40-60) | 47 (35-55) | 0.589 |
| **Mean gradient (mmHg)** | 13 (11-18) | 15.5 (11-20) | 0.390 |
| **Planimetric MVA (cm²)** | 1.0 (0.9-1.2) | 1.0 (0.85-1.2) | 0.528 |
| **MVA PHT (cm²)** | 1.1 (0.98-1.2) | 1.0 (0.9-1.3) | 0.715 |
| **Wilkins score** | 8 (7-8.5) | 8 (7.5-9) | 0.144 |

*TTE: Transthoracic echocardiography, sPAP: Systolic pulmonary artery pressure, LA: Left atrium, MVA: Mitral valve area, PHT: Pressure halftime*

## Discussion

This study analyzed the predictors of mitral restenosis in patients who underwent PMBV. It demonstrated that PMBV was performed in eligible patients with procedural success rate of 87.0%. According to our study, 21 out of 178 patients developed mitral restenosis following successful PMBV. Additional to that, patients who had restenosis after PMBV had significantly higher value in PLT indices such as PLT, PCT and MPV.

PMBV has been a choice for the treatment of patients with symptomatic significant mitral stenosis with favorable mitral valve morphology. Despite its favorable outcomes, studies have revealed high rates of restenosis with adverse clinical events in patients who underwent successful PMBV[18-21]. According to a study conducted by Farhat et al.[22], incidence of restenosis after PMBV has been reported between 3% and 70% in one to three years. They also demonstrated that the risk of restenosis

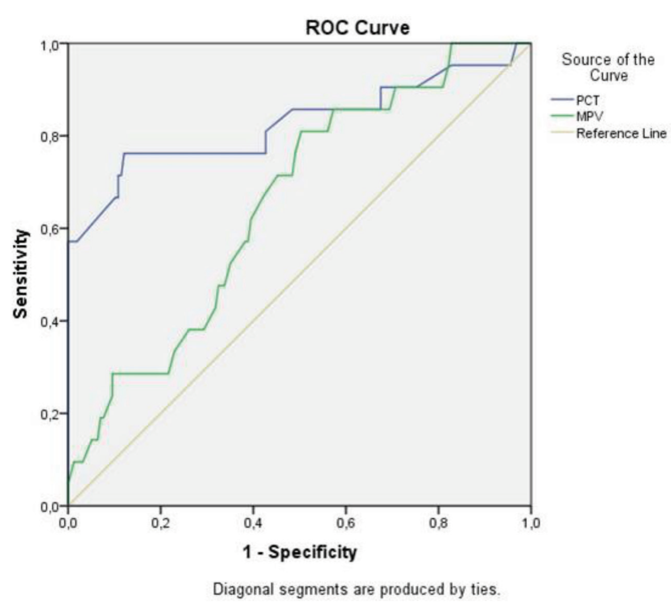


**Figure 1.** ROC analysis was conducted to determine the optimal MPV and PCT cut-off values to indicate restenosis

*ROC: Receiver operating characteristic, MPV: Mean platelet volume, PCT: Platelecrit* increased progressively during follow-up of these patients (77% at 10 years, 46% at 15 years and 18% at 18 years, respectively). In another study by Hernández et al.(2), older patients (mean age 53 years) had higher rate of restenosis (39% restenosis rate at 7 years). Outcome of those studies demonstrated that major predictor factor for restenosis as WS, especially pre-procedural WS ≥8 was associated with higher risk of restenosis. Previous studies also reported that post-procedurally estimated MVA and restenosis were

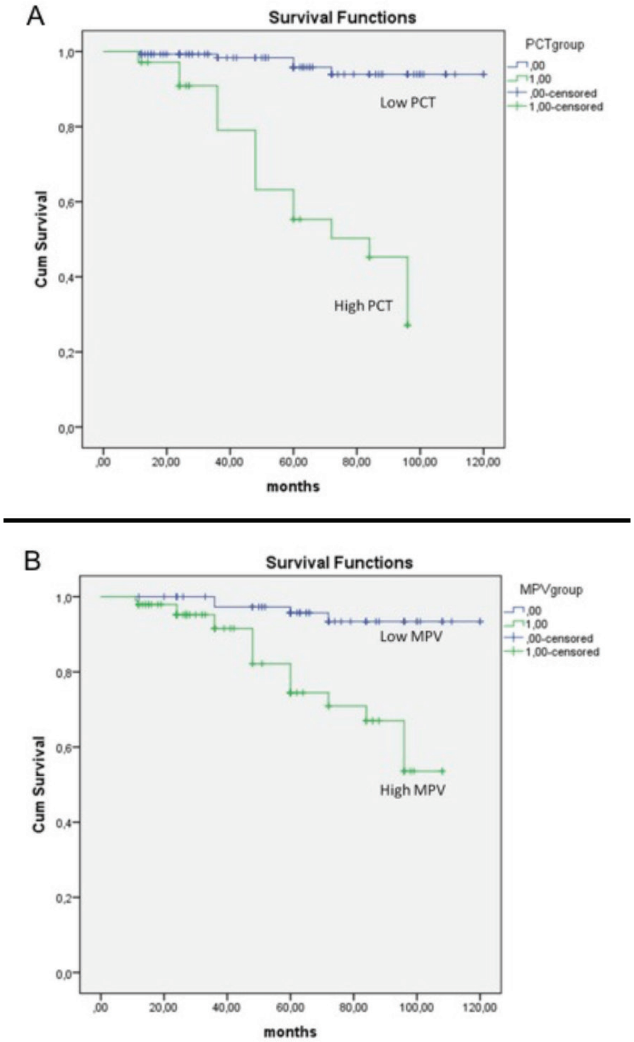


**Figure 2.** A Kaplan-Meier survival analysis also revealed that long term restenosis rate was found to be significantly higher in patients with higher PCT **(A)** and MPV **(B)** values
*PCT: Platelecrit, Cum: Cummulative, MPV: Mean platelet volume*

**Table 4.** Procedural and post-procedural data for the groups. Restenosis (+) group includes data of redo PMBV and restenosis (-) group includes data of PMBV

| | Restenosis (-) (n=157) | Restenosis (+) (n=21) | p value |
|---|---|---|---|
| **Post-procedural TTE** | | | |
| **Ejection fraction (%)** | 60 (60-65) | 60 (60-65) | 0.967 |
| **sPAP (mmHg)** | 30 (25-38) | 35 (29-40) | 0.281 |
| **LA diameter (cm)** | 4.2 (3.9-4.5) | 4.2 (4.0-4.8) | 0.174 |
| **Planimetric MVA ($cm^2$)** | 1.8 (1.6-2.0) | 1.8 (1.6-1.9) | 0.568 |
| **MVA PHT ($cm^2$)** | 1.8 (1.6-2.0) | 1.8 (1.65-2.05) | 0.938 |
| **Mean gradient (mmHg)** | 5 (4-6) | 6 (5-7) | **0.004** |
| **Balloon diameter (mm)** | 28 (28-28) | 28 (26-28) | 0.254 |
| **Balloon inflation** | | | |
| 1 time | 24 (18.2) | 2 (11.8) | 0.569 |
| 2 times | 84 (63.6) | 10 (58.8) | |
| 3 times | 22 (16.7) | 5 (29.4) | |
| 4 times | 2 (1.5) | 0 (0) | |
| **Procedural need for emergent surgery** | 9 (5.7) | 0 (0) | - |
| Severe MR (n, %) | 5 (3.2) | 0 (0) | - |
| Tamponade (n, %) | 4 (2.5) | 0 (0) | - |
| **Emergent intervention** | | | |
| MVR (n, %) | 8 (5.1) | 0 (0) | - |
| Comissurotomy (n, %) | 1 (0.6) | 0 (0) | - |
| **Procedural success (n, %)** | 138 (87.9) | 17 (81.0) | 0.277 |

*TTE: Transthoracic echocardiography, sPAP: Systolic pulmonary artery pressure, LA: Left atrium, MVA: Mitral valve area, PHT: Pressure half time, MR: Mitral regurgitation, MVR: Mitral valve replacement, n: Number*
*Important p values are written in bold*

**Table 5.** ROC analysis of platelet indices for mitral restenosis

| | | | | | |
|---|---|---|---|---|---|
| **MPV** | **AUC** | **95% CI** | **Cut-off** | **Sensitivity** | **Specificity** |
| | 0.656 | 0.541 - 0.770 | >9.65 | 81.0 | 49.7 |
| **PCT** | **AUC** | **95% CI** | **Cut-off** | **Sensitivity** | **Specificity** |
| | 0.826 | 0.700 - 0.952 | >0.241 | 76.2 | 87.9 |

*ROC: Receiver operating characteristic, MPV: Mean platelet volume, PCT: Platelecrit, AUC: Area under curve, CI: Confidence interval* closely related to long-term clinical results of PMBV[23,24]. On this basis, they have hypothesized that complete commissurotomy resulting in larger MVA might prevent fibrous fusion of split commissures and restenosis[25]. Similar findings were also documented by Ruiz et al.[26], they demonstrated that old age, heavy calcification, high WS, and suboptimal opening of mitral valve were major predictive factors for restenosis.

In our study, major predictors of restenosis were high levels of WS, previous history of mitral valve intervention and higher levels of post-procedurally estimated trans-mitral gradient, which were compatible with previous studies. Additionally, we also demonstrated a strong association between higher values of pre-procedural PLT indices, including PLT count, MPV and PCT and rate of restenosis. To the best our knowledge, this is the first study in literature which revealed a relationship between PLT indices and mitral restenosis.

Evidence from several studies has shown that MPV is a reliable method for measuring PLT size which indicates PLT function. Compared to normal size counterparts, larger PLT has higher hemostatic activity and contributes to the development of increased pro-coagulant activity of PLT, thrombosis and tromboembolism. According to those studies, severe rheumatic mitral stenosis is associated with increased risk for pro-coagulant activity of PLT and thrombosis. The presence of endothelial dysfunction and turbulent blood flow as a result of mitral valve stenosis were possible underlying mechanisms[27-29]. Similar results were demonstrated by Erdogan et al.[30] in patients with rheumatic mitral stenosis. According to their study, patients with rheumatic mitral stenosis had a higher MPV than healthy controls [9.05±1.26 vs 7.56±0.74 fl, $p<0.001$] and those patients had higher PLT activity than controls[30]. In another study, Chen et al.[11] reported increased peripheral venous PLT P-selectin expression in patients with moderate to severe rheumatic mitral stenosis compared to healthy counterparts. They also demonstrated a relationship between the amount of regional left atrial PLT P-selectin expression and the severity of mitral stenosis.

Calculated PCT in a blood sample is known to be an indicator of PLT mass in the blood just as hematocrit which is an indicator of total erythrocyte mass in the blood. Compared to total PLT count, PCT is turned out to be the best parameter in terms of estimating the PLT activity[31]. These findings in these studies demonstrate the close relationship between PLT activity and severity of rheumatic involvement of mitral stenosis.

Apart from above mentioned parameters, our study has also revealed that patients who underwent redo PMBV has a higher incidence of AF, which has been reported as a strong predictor of late outcome in series of balloon and surgical commissurotomy procedures[32,33]. The literature showed the association between increased PLT activation and AF. However, the studies proved that this activation was mostly related to MVA and severity of mitral valve disease[34]. Therefore, it was suggested that PLT activity, spontaneous echo contrast, mitral valve disease and AF were closely related to each other and AF seemed to be not the cause of increased PLT activity but the severity of mitral valve disease corresponded with the activation[35].

## Study Limitations

There were several limitations in our study. First, and foremost, the retrospective nature of the study inherently limits the generalizability of our results. Another limitation of our study was relatively a small sample size with a short follow-up time. Although clinical characteristics and immediate post-procedural outcomes of our study were similar to the previous studies, our study population consisted of relatively young patients compared to those studies. Outcomes of this study may not be extrapolated to older patients with less favorable valve characteristics. In addition, we did not assess novel markers of PLT activation status such as soluble P-selectin or soluble CD-40 ligand. Further prospective studies with novel PLT activation markers should be implemented to clarify the relationship between PLT indices and the incidence of mitral restenosis following PMBV.

## Conclusion

Estimated WS and post-procedural MVA (MVA ≤1.5 $cm^2$) seem to be still superior than other parameters to predict restenosis after PMBV. However, PLT indices including PLT count, MPV and PCT might be feasible and easy parameters to predict possible restenosis after PMBV.

### Ethics

**Ethics Committee Approval:** This study was approved by the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee (decision no: 2020/58, date: 18.08.2020).

**Informed Consent:** Informed consent was obtained from all patients in accordance with a protocol.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: Ö.T., A.A.Ş., Ö.Ç., Design: Ö.T., A.A.Ş., Ö.Ç., Data Collection or Processing: Ö.T., M.D., Analysis or Interpretation: A.A.Ş., M.D., S.K., Literature Search: Ö.T., M.D., Writing: Ö.T., A.A.Ş., M.D., S.K., Ö.Ç.

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Research Article

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# Evaluation of Ventricular Polarization in Noncompaction Cardiomyopathy with Electrocardiography in a Different Perspective

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## Abstract

**Objectives:** Noncompaction cardiomyopathy (NCCM) is a rare genetic form of cardiomyopathy. Morphologically, it consists of a thickened two-layer myocardial structure (noncompacted-compacted layers.). In NCCM, especially in highly symptomatic cases, abnormal basal electrocardiographic (ECG) patterns can be observed at all stages of atrial and/or ventricular depolarization and repolarization. In recent studies, it has been shown that increased QT duration, fragmented QRS pattern, increased spatial QRS-T angle could be predictive concerning ventricular arrhythmias in NCCM. We aimed to show the relationship (if any) between the parameters related to ventricular depolarization and repolarization, which are QT variability/dispersion (QTd), TPe, TPe/QT ratio, "the index of Cardiac-Electrophysiologic Balance (iCEB)" and NCCM.

**Materials and Methods:** Thirty NCCM patients and 31 healthy volunteers were included in this cross-sectional, case-control study. ECG parameters related to ventricular polarization were evaluated for all participants.

**Results:** In our study, we observed that TPe, corrected TPe (cTPe), TPe/QT, TPe/corrected QT (cQT) and cTPe/cQT values were significantly lower in NCCM patients compared to controls (all p values <0.005). QTd and corrected QTd (cQTd) values are also relatively low in NCCM (p>0.05).

**Conclusion:** We found a significant relationship between NCCM and TPe, cTPe, TPe/QT, TPe/cQT, cTPe/cQT parameters. It can be thought that our study contributed to the literature with the present findings and it may also be a guide for clinical trials to investigate the relationship of these parameters with ventricular arrhythmias in NCCM.

**Keywords:** Arrhythmia, electrocardiography, cardiomyopathy

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## Introduction

Noncompaction cardiomyopathy (NCCM) morphologically consists of increased trabeculation and a thickened two-layer myocardial structure[1,2]. Congestive heart failure, arrhythmias, thromboembolic events can be seen in NCCM[3]. However, in recent years, asymptomatic cases have increased with the increase of screening[4]. Especially in highly symptomatic cases, abnormal electrocardiogram (ECG) patterns such as atrial fibrillation, atrioventricular block, bundle branch blocks, and Wolff-Parkinson-White pattern were observed. ECG abnormalities can be observed at all stages of atrial and/or ventricular depolarization and repolarization[5,6]. Findings of left ventricular hypertrophy (LVH), PR and QT prolongation, and T wave changes can be counted among other ECG changes[7]. Beta-blocker therapy is considered as a safe treatment for the suppression of arrhythmias, especially in the group with heart failure. Class 3 antiarrhythmic drugs can also be used in appropriate conditions[8]. Implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) treatment modalities can also be applied within the clinical indications in the follow-up of the patients[9].

In recent studies, it has been shown that increased QT duration, fragmented QRS (fQRS) pattern, increased spatial QRS-T angle could be predictive concerning ventricular arrhythmias, morbidity and mortality in NCCM[10,11].

In studies conducted related to ventricular polarization abnormalities and arrhythmic events, it was stated that the QTd and the TPe could be used as a biomarker for torsades de pointes risk assessment[12-14]. Similarly, the TPe/QT ratio can be used as a biomarker because it gives information about the transmural dispersion of LV repolarization[15-17]. In 2016, Chua et al.[18] examined the ECG of patients who had a history of sudden cardiac arrest (SCA) and showed that TPe value could be an independent predictor of SCA. It was also stated that the values of QT and TPe should be corrected according to the heart rate. As a result of the measurements made using the Bazett formula, it was concluded that the cTPe above 90 ms increased the risk almost three times. Based on electrophysiological studies, in 2013, it has been revealed that the QT/QRS ratio can be used as a new biomarker to detect cardiac arrhythmias. Such an inference has been made because changes in the QT time are proportional to changes in the effective refractory period (ERP) time and changes in the QRS wave duration are proportional to conduction velocity. This biomarker is named as "iCEB"[19].

Based on these studies and with the plan to look at the parameters that have not been studied before at about NCCM, in our article, it is aimed to show the relationship (if any) between NCCM and the parameters related to ventricular depolarization and repolarization which are QTd, TPe, TPe/QT ratio and iCEB.

## Materials and Methods

Our study is a cross-sectional, case-control study. Thirty NCCM patients (18-65 ages) who were diagnosed through cardiac magnetic resonance (CMR) (using Peterson Criteria) were included[20]. Ischemic cardiomyopathy, peripartum cardiomyopathy, chronic alcohol use, chemotherapeutic drug use with known cardiotoxic effect, body mass index >35 kg/m$^2$, infiltrative diseases, endocrine disorders, acute/chronic kidney disease, myocarditis, moderate/severe heart valve diseases, cardiac intervention/operation (pacemaker, ICD, CRT implantation, left ventricular assist device, heart transplantation) history, and reversible situations which could cause left ventricular noncompaction were determined as exclusion criteria. All the patients were in sinus rhythm; LVH, cardiac blocks, antiarrhythmic drug usage other than beta-blockers, antihistamine, tricyclic antidepressants, and antipsychotics usage were also excluded. Beta-blocker usage could not be excluded due to the treatment being included in the optimal medical treatment for heart failure. The control group consisted of age- and sex-matched 31 healthy volunteers. Informed consent was obtained from all patients and local ethics committee approval was received (Ege University Ethics Committee, with date: 8/8/17, number: 17-6/12).

Standard echocardiographic measurements were made in reference with 2015 ASE (American Society of Echocardiography) guideline[21]. NC/C ratio was calculated by echocardiography at the end of systole with the Jenni criterion[22]. Parameters related to CMR were obtained from patients' hospital reports.

## Electrocardiographic Evaluation

The standard 12-lead surface ECGs of patients were obtained at rest in the supine position (10 mV/mm and 50 mm/s paper speed; with recorder Nihon Kohden, Japan). After scanning, all ECGs were analyzed in a digital platform with x400 magnification to diminish the error. Measurements of ECGs were performed by two separate cardiologists. Heart rate and QRS duration data were taken from the automated ECG report. The QT interval was calculated from the onset of the QRS complex to the end of the T wave in as many leads as possible (minimum and maximum values of QT were also recorded.). TPe interval was calculated from the peak point to the end of T wave in V5, followed by other precordial leads if V5 was not appropriate (Figure 1). The QT and TPe intervals were corrected for heart rate using the Bazett formula ($QT/\sqrt{RR}$-$TPe/\sqrt[3]{RR}$)[18]. QTd was calculated as the difference of QT maximum ($QT_{max}$) and minimum ($QT_{min}$) values and corrected QTd (cQTd) was calculated also as the difference in corrected QT maximum ($cQT_{max}$) and corrected QT minimum ($cQT_{min}$). TPe/$QT_{max}$, cTPe/$cQT_{max}$, $QT_{max}$/QRS (also named as iCEB), $cQT_{max}$/QRS (also named as iCEBc) were other measured parameters[19]. iCEB was calculated by the formula using $QT_{max}$, $cQT_{max}$, and QRS duration values in our data. Subjects with U waves and ECGs that were not suitable for evaluation were excluded.

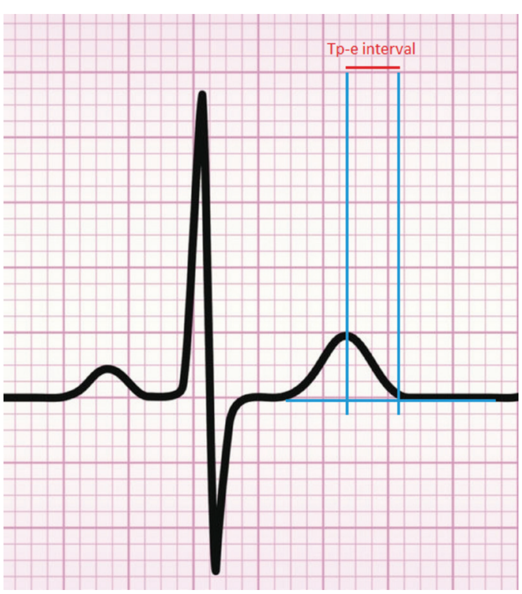


**Figure 1.** Measurement of TP-e interval
*TP-e: T-peak to T-end*

### Statistical Analysis

Statistical analysis was carried out by using SPSS software (version 22.0, SPSS Inc., Chicago, IL, US). Continuous variables were expressed as median while categorical variables were shown as a percentage (%). The Student t-test or Mann-Whitney U test were used for continuous variables, and Fisher's exact test or chi-square test, whichever was suitable, was used for categorical variables. Values with p<0.05 were considered statistically significant.

## Results

Basal characteristics of the study population are summarized in Table 1. There were no significant differences between the groups regarding age, gender and body surface area (BSA). In the patient group, two patient had diabetes mellitus (DM) and nine patients had hypertension (HT). Beta blocker usage rate was %78.1 for the patients (The beta blocker agents used by patients were carvedilol and metoprolol. The maximum doses were 25 mg twice a day for carvedilol and 100 mg once a day for metoprolol.).

In the patient group, the mean value of left ventricular ejection fraction was 43.4, and significantly lower than in the control group (p<0.001). Left atrium, left ventricular end-diastolic and end-systolic diameters (LVEDD-LVESD) were higher in the patient group (p<0.05, only for LVEDD p=0.166). The mean heart rates were similar (p=0.989) but the QRS duration was significantly higher in the patient group (p=0.006). Other ECG findings are showed in Table 2.

Although the mean $QT_{max}$, $QT_{min}$, QTd, and also their corrected measurements ($cQT_{max}$, $cQT_{min}$, cQTd) were higher and iCEB and iCEBc were lower in the patient group compared to the control group, no significant difference was observed (p>0.05). TPe and TPe related parameters, which were cTPe, TPe/QT ratio, TPe/cQT ratio, and cTPe/cQT ratio, were observed to be significantly higher in the patient group compared to the control group (all p values <0.05).

## Discussion

In the studies carried out to date to determine the electrocardiographic features of the NCCM and the risk of arrhythmia, primarily parameters such as fQRS and QT duration were investigated and their relationship with arrhythmia and prognosis was determined[10,23]. Besides, the search for new electrocardiographic parameters concerning risk analysis in NCCM continues in recent years like T-wave amplitudes during ventricular repolarization in lead aVR (TaVR) and spatial QRS-T angle[11,24].

In NCCM, heart rate changes can be monitored also with the effect of accompanying pathologies and the antiarrhythmic drug use. Bugan and Cekirdekci[25] investigated the cardiac autonomic features of NCCM and possible effects on mortality and achieved abnormal results in heart rate variability and heart rate turbulence.

QTd shows heterogeneity in ventricular repolarization secondary to changes in action potential duration and activation time. In a meta-analysis conducted by Bazoukis et al.[26], as a result of the analysis of heart failure and coronary artery patients, QTd value was shown to have prognostic significance concerning arrhythmic events.

**Table 1.** Characteristics of the study population

| | Patient (n=30) | Control (n=31) | p |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Age (year) | 35.96±13.12 | 40.48±14.80 | 0.440 |
| Gender, male, n, % | 19 (63.3%) | 19 (61.3%) | 0.903 |
| BMI (kg/m$^2$) | 24.38±4.62 | 23.13±2.91 | 0.018 |
| BSA (m$^2$) | 1.79±0.23 | 1.85±0.19 | 0.129 |
| Systolic BP (mmHg) | 118.20±22.51 | 116.84±11.93 | 0.041 |
| Diastolic BP (mmHg) | 70.15±14.30 | 71.16±8.55 | 0.363 |
| Diabetes mellitus, n, % | 2 (6.3%) | 0 (0.0%) | 0.476 |
| Hypertension, n, % | 9 (28.1%) | 0 (0.0%) | 0.036 |
| Beta blocker usage, n, % | 25 (78.1%) | 0 (0.0%) | 0.045 |
| **Echocardiography** | | | |
| Left atrium (mm) | 3.86±0.71 | 3.20±0.33 | 0.001 |
| LVEDD (mm) | 5.52±0.94 | 4.53±0.42 | 0.166 |
| LVESD (mm) | 4.36±1.14 | 2.88±0.43 | 0.001 |
| IVS (mm) | 1.02±0.15 | 0.87±0.09 | 0.001 |
| E/A | 1.45±0.78 | 1.52±0.34 | 0.432 |
| LVEF Simpson (%) | 43.4±16.1 | 64.2±5.7 | <0.001 |
| NC/C thickness ratio | 2.72±0.37 | | |
| **Cardiac MR** | | | |
| NC/C thickness ratio | 2.88±0.48 | | |

*BMI: Body mass index, BSA: Body surface area, BP: Blood pressure, LVEDD: Left ventricle end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, IVS: Interventricular septum, LVEF: Left ventricle ejection fraction, NC: Noncompacted layer, C: Compacted layer, E: Early diastole, A: Late diatole, MR: Magnetic resonance, SD: Standard deviation, n: Number*

**Table 2.** Electrocardiographic parameters

| | Patient (n=30) | Control (n=31) | p |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| **Heart rate (/min)** | 74.2±14.28 | 74.65±10.32 | 0.989 |
| **QRS (ms)** | 95.73±13.83 | 86.06±10.19 | 0.006 |
| **$QT_{max}$ (ms)** | 387.20±36.27 | 371.29±25.23 | 0.123 |
| **$cQT_{max}$ (ms)** | 426.70±34.21 | 412.68±33.01 | 0.161 |
| **$QT_{min}$ (ms)** | 365.33±37.71 | 351.81±24.67 | 0.233 |
| **$cQT_{min}$ (ms)** | 402.46±35.04 | 391.05±32.45 | 0.290 |
| **QTd (ms)** | 21.87±8.61 | 19.48±5.07 | 0.324 |
| **cQTd (ms)** | 23.24±9.52 | 21.62±5.69 | 0.670 |
| **QT/QRS (iCEB)** | 4.11±0.60 | 4.37±0.61 | 0.210 |
| **cQT/QRS (iCEBc)** | 4.53±0.63 | 4.84±0.60 | 0.099 |
| **TPe (ms)** | 79.93±9.04 | 69.32±8.32 | <0.001 |
| **cTPe (ms)** | 88.27±10.90 | 77.32±11.74 | 0.001 |
| **TPe/QT** | 0.207±0.026 | 0.188±0.026 | 0.008 |
| **TPe/cQT** | 0.188±0.026 | 0.168±0.022 | 0.003 |
| **cTPe/cQT** | 0.201±0.024 | 0.181±0.024 | 0.004 |

*$cQT_{max}$: Corrected $QT_{max}$, $cQT_{min}$: Corrected $QT_{min}$, QTd: QT dispersion, cQTd:corrected QT dispersion, for QT/QRS and TPe/QT ratios $QT_{max}$ values were used, for cQT/QRS and TPe/cQT ratios $cQT_{max}$ values were used, SD: Standard deviation, n: Number*

It was also noted that this value was relatively high in patients with sudden cardiac death (SCD). In our study, QTd and cQTd values were relatively high compared to the controls ($p>0.05$). In the study conducted by Lu et al.[19] on the iCEB, which is a parameter related to the balance of ventricular depolarization and repolarization, the predictive properties of this new parameter were demonstrated for drug-related cardiac arrhythmias. In our study, there were no significant differences in iCEB and iCEBc values in NCCM patients compared to the control group.

TPe shows transmural dispersion of ventricular repolarization more accurately compared to the QT interval. In a study conducted by Chua et al.[18], which investigated SCA patients, it has been shown that the cTPe value obtained after the correction of the TPe value according to heart rate using the Bazett or Fridericia formulas is predictive in terms of SCD, and this value over 90 ms (with Bazett formula) increases this risk three times. In our study, the mean value of cTPe was 88.27±10.90 and significantly higher than in the control group ($p=0.001$), and similarly TPe values were significantly higher ($p<0.001$). TPe/QT is another ECG parameter that can give an idea about transmural dispersion of left ventricular repolarization to be useful in predicting malignant cardiac arrhythmias in various diseases such as slow coronary flow, acute myocarditis, frequent outflow tract premature ventricular complexes[16,17,27]. In our study, TPe/QT, TPe/cQT, and cTPe/cQT values were significantly higher than in the controls (all p values <0.05).

This is the first study to search the electrocardiographic features related to ventricular depolarization and repolarization in terms of QTd, iCEB, TPe and TPe related parameters. In our study, we aimed to show the relationship (if any) between NCCM and the electrocardiographic parameters related to ventricular depolarization/repolarization, which are QTd, TPe, TPe/QT ratio and iCEB. We showed a significant relationship with NCCM and TPe, cTPe, TPe/QT, TPe/cQT and cTPe/cQT.

### Study Limitations

In our study, we were able to evaluate a limited number of patients, also with the effect of NCCM which is a rare disease. Patients had some comorbidities like HT and DM. Because they are included in the optimal treatment protocol, some of the patients were using beta-blockers. Beta-blocker usage and comorbidities may have affected the results related to the electrocardiographic parameters.

## Conclusion

We found a significant relationship between NCCM and TPe, cTPe, TPe/QT, TPe/cQT, cTPe/cQT parameters. We also observed that the values of QTd and cQTd were higher in NCCM compared to the control group. It can be thought that our study contributed to the literature with the present findings. The parameters which we investigated in our study and their relationship with arrhythmias in NCCM can be researched in further studies. Also, there is a need for further studies on the subject, with a larger number of patients. Thus, subgroup analysis can also be performed according to heart failure classification.

### Ethics

**Ethics Committee Approval:** This study was approved by Ege University Ethics Committee, (date: 8/8/17, number: 17-6/12).

**Informed Consent:** Informed consent was obtained from all patients.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: O.A., İ.A., Concept: O.A., İ.A., Design: O.A., Data Collection or Processing: O.A., Analysis or Interpretation: O.A., İ.A., Literature Search: O.A., İ.A., Writing: O.A., İ.A.

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# Evaluation of the Global Longitudinal Strain in FMF: In Relation with Duration of Illness

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## Abstract

**Objectives:** The aim of this study is to investigate the effects of Familial Mediterranean Fever (FMF) on cardiac function via speckle tracking echocardiography (ECG) in pediatric FMF patients without cardiac symptoms and to compare speckle tracking ECG results with the conventional echocardiographic outcomes.

**Materials and Methods:** A total of 50 FMF children aged between 5 and 19 years and 50 healthy children adjusted by age were evaluated for inclusion. Conventional ECG of each participant was performed to investigate mechanical myocardial function. Global longitudinal strain (GLS) measurements were performed using 2D speckle tracking ECG.

**Results:** The mean duration of illness among FMF patients was 4.6±3.1 years. There was no statistically significant relationship between sex and duration of illness ($p>0.05$). GLS values measured by two-dimensional speckle tracking between the groups were significantly lower in individuals diagnosed with FMF compared to the control group (-18.0±2.0/-22.5±2.0; $p<0.001$). The relationship between disease duration and left ventricle-GLS values of individuals diagnosed with FMF was evaluated by spearman correlation analysis. It was observed that left ventricle-GLS values decreased statistically with increasing disease duration.

**Conclusion:** Speckle tracking ECG can provide the chance to reveal subclinical ventricular dysfunction before cardiac dysfunctions progress in children with FMF.

**Keywords:** Familial Mediterranean Fever, left ventricular function, speckle tracking echocardiography, strain

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## Introduction

Familial Mediterranean Fever (FMF) is a hereditary auto inflammatory disease with unknown cause and characterized by attacks of fever, peritonitis, synovitis and pleurisy in the majority of patients, while some may also exhibit skin lesions, vasculitis and amyloidosis[1-5]. It has been known for quite some time that the disease spreads into the gastrointestinal system, liver and spleen; however, the involvement of myocardial tissue is a relatively recent discovery[6,7]. Although the term cardiomyopathy is not used to define the changes caused by FMF, the disease may mildly affect systolic and diastolic function[8]. Conventional echocardiography (ECG) is the most commonly used method in the evaluation of heart involvement and left ventricle function in patients with FMF[8]. Besides, subclinical FMF patients are generally considered normal with conventional ECG and pulsed wave Doppler. Pulsed wave Doppler tissue imaging utilizes both global and regional myocardial function to unveil subclinical cases and examine left ventricular myocardial segments[9,10]. Nevertheless, this method cannot discriminate between the movement of myocardial tethering and translational motion and it is affected by the rotational movement of the heart. Therefore, a new technique has been developed: strain and strain rate ECG[11,12]. Strain and strain rate can be determined using speckle tracking ECG (STE). STE emerged as a technique that could determine right and left ventricular function more reliably and comprehensively compared to previous iterations of the ECG technique[13]. Being able to single-handedly determine cardiologic characteristics which would normally require various methods is the most critical advantage. Other distinguishing features of the STE method include angle-independent use, high frame-rate, less noise-interference, and low inter and intra-operator variance[14].

While the cardiac and left ventricle functions of FMF patients that were measured via tissue Doppler and strain imaging have been previously reported respectively, there are only a few studies which have utilized the STE technique. The aim of this study is to investigate the effects of FMF on cardiac function via STE in pediatric FMF patients without cardiac symptoms and to compare STE results with conventional echocardiographic (CE) outcomes.

## Materials and Methods

All patients and control groups were enrolled in a duration between January 2016 and December 2017 and follow-up provided by the Pediatric Rheumatology Department of İstanbul Medical Faculty. A total of 50 FMF children aged between 5 and 19 years and 50 healthy children adjusted by age were evaluated for inclusion. The diagnosis of familial Mediterranean fever was made considering the Tel-Hashomer criteria[15]. When the genetic mutations of the patients were examined, 17 patients were homozygous (MEFV 694 V), eight patients were heterozygous, and 24 patients were compound heterozygous. Patients who had fewer than three FMF attacks per year were included. All FMF patients were using colchicine at a dose of 1-1.5 mg/day, and during echocardiographic evaluation, the disease was in remission period in all individuals. Medical history, disease duration, number of attacks, physical examination, laboratory and echocardiographic findings of FMF patients were recorded. Being over 18 years of age, having non-FMF inflammatory disease, proteinuria, acute attacking, being a smoker, having congenital heart disease/acquired, arrhythmia, moderate or severe heart valve abnormalities, presence of complete bundle branch block, poor echocardiographic evaluation due to poor echogenicity, regional patients with wall motion defect and left ventricular ejection fraction (LVEF) below 55% were considered as exclusion criteria from the study. LVEF (≥%55) and Wall motion score (WMSI) (=1.0) were considered as normal left ventricular systolic function. Left ventricular functions were evaluated using conventional ECG method and STE method.

### Conventional Echocardiography

ECG of each participant was performed to investigate mechanical myocardial function. Conventional ECG was performed through the parasternal and apical windows by using a Philips IE33 instrument and X5-1 transthoracic probe with the patients in the left lateral position (2-dimensional, M-mode, Doppler ECG). ECG was begun after at least 15 minutes of rest and according to the standard images and techniques in the American and European Cardiovascular Imaging Association guideline[16]. All evaluations were performed by a single researcher. M-mode images were obtained from between the mitral valve and papillary muscle on the parasternal long axis. From the parasternal long-axis view of the left ventricule (LV) end-diastolic and end-systolic diameters, interventricular septal and posterior wall thicknesses were expressed in millimeters. We measured LV end-systolic and end-diastolic volumes from the apical 4-chamber view. LVEF was calculated using the modified Simpson biplane method. LV filling was evaluated by pulse wave Doppler from the apical 4-chamber view with the sample volume position at the tips of the mitral valve, and velocities in early (E) and late (A) diastole were recorded, in addition to the calculation of the E/A ratio.

### Strain Echocardiography Measurements

Longitudinal global strain (LGS) measurements were performed by using 2D speckle tracking ECG (STE). In these analyses, Philips IE33 and QLAB-CMQ software were used. Measurements were completed using images containing at least 4 cardiac cycles during short apnea period from apical (4 space) windows. The wall motion of each LV segment was visually evaluated on the basis of motion and systolic thickening in a 17-segment model (three segments per wall). Each segment was determined as a conventional four-point scale (1, normokinetic 2, hypokinesia; 3 akinesia; 4, dyskinesia). WMSI was calculated by taking the average value of all segments of each location[17]. When the quality was insufficient for analysis, the patient was excluded from the study. The end of diastole was defined in the peak R wave of the electrocardiogram, while the end of systole was defined as the aortic valve closing time. Endocardial borders were observed within the frame of 2D images at the end of systole. Manual adjustments were made, if necessary, to ensure correct tracking and to close all LV wall thickness for 2D speckle viewing width.

All participants gave their written informed consent to the study, which was approved by our Institutional Ethical Committee in accordance with the Declaration of Helsinki, from the Clinical Trials Ethics Committee of İstanbul University (decision no and date: 951 and 11.05.2015).

### Statistical Analysis

All analyses were performed on SPSS 19. Normally distributed continuous variables were described as mean ± standard deviation. Categorical data were described as frequency (percentages). We assessed differences between the groups with the t-test for normally distributed variables and with the chi-square test for categorical data and proportions. The Spearman correlation coefficients were calculated for continuous variables regarding normality. The Kolmogorov-Smirnov test was applied to analyze normality of the data. The Mann-Whitney U test or Student's t-test were applied to compare unpaired samples as needed. $P<0.05$ values were accepted as statistically significant.

## Results

Fifty of the 100 individuals included in the study were diagnosed as FMF, and their clinical and demographic characteristics are shown in Table 1. There was no difference in age and gender between the groups. While 21 of the 50 patients diagnosed with FMF were male (43%), 16 of the 50 people in the control group were male (33%). The mean age of the individuals diagnosed with FMF was 12.8±4.2 years and the mean age of the individuals in the control group was 12.1±3.6 years. There was no statistical difference between the groups in terms of body mass index. Similarly, there was no statistical difference between the two groups in heart rate, systolic blood pressure and diastolic blood pressure at admission. When laboratory tests were compared in both groups, creatinine, hemoglobin, hematocrit, leukocyte count, sedimentation, C-reactive protein and fibrinogen values were statistically similar. In addition, while all of the individuals diagnosed with FMF were using colchicine, the mean disease duration was determined as 4 (2-6) years (Table 1).

In the conventional echocardiographic examination, individuals who were diagnosed with FMF and control group values were compared in terms of LVEF, left ventricular end diastolic diameter, left ventricular end systolic diameter, interventricular septum thickness-diastolic (IVSTd), posterior wall thickness (PWT), left atrium (LA), stroke volume, WMSI and diastolic parameter indicators, E wave, A wave, E/A ratio, isovolumic relaxation time (IVRT), and there was no statistical difference between Lateral E', Lateral A' and E'/A' ratio.

Global longitudinal strain (GLS) values measured by two-dimensional speckle tracking between the groups were significantly lower in individuals diagnosed with FMF compared to the control group (-18.0±2.0/-22.5±2.0; p<0.001) (Table 2 / Figure 1).

**Table 1.** Clinical demographic characteristics of Familial Mediterranean Fever patients and control group

| Number of patients (n) | FMF (n=50) | Controls (n=50) | p |
|---|---|---|---|
| Age, years | 12.8±4.2 | 12.1±3.6 | 0.412 |
| Sex (male, %) | 21 (43%) | 16 (33%) | 0.295 |
| BMI, kg/m$^2$ | 19.0±2.7 | 20.1±4.1 | 0.115 |
| Disease duration (year) | 4 (2-6) | - | - |
| Colchicine, n (%) | 50 (100%) | - | - |
| Heart rate (minute) | 85.8±12.4 | 82.4±11.8 | 0.168 |
| Systolic blood pressure (mmHg) | 106.5±10.3 | 108.1±9.0 | 0.414 |
| Diastolic blood pressure (mmHg) | 67.5±7.0 | 68.5±5.9 | 0.474 |
| Creatinine (mg/dL) | 0.7±0.1 | 0.8±0.1 | 0.681 |
| Hemoglobin (g/dL) | 13.6±1.5 | 14.0±1.7 | 0.299 |
| Hematocrit (%) | 40.8±4.7 | 42.5±5.4 | 0.451 |
| Leukocyte, x10$^3$/mm$^3$ | 6.4±2.2 | 6.1±2.1 | 0.599 |
| Sedimentation, mm/h | 9.4±4.3 | 8.0±3.9 | 0.098 |
| CRP, mg/dL | 5.2±2.2 | 4.8±2.1 | 0.314 |
| Fibrinogen, gr/L | 2.6±0.9 | 2.7±0.8 | 0.221 |

*FMF: Familial Mediterranean Fever, BMI: Body mass index, CRP: C-reactive protein, n: Number*

The relationship between disease duration and left ventricular GLS (LV-GLS) values of individuals diagnosed with FMF was evaluated by the spearman correlation analysis. It was observed that LV-GLS values decreased statistically with increasing disease duration (r=0.608/ p<0.001) (Figure 2).

### Reproducibility

A total of 15 patients were randomly selected for inter and intra-observer variability analysis. Compatibility of LV-GLS with and between observers and WMSI values was calculated.

The intra-class correlation coefficient for inter-observer and intra-observer variability was, respectively: 0.91 [95% confidence interval (CI), 0.88–0.94] and 0.93 (95% CI, 0.89–0.96) for LV-GLS; 0.89 (95% CI, 0.85–0.95) and 0.92 (95% CI, 0.88–0.95) for the WMSI.

## Discussion

In the study, the GLS value of individuals with normal left ventricular systolic function and diagnosed with FMF was analyzed by 2D speckle tracking method:

1. In the GLS examination, strain values were lower in individuals diagnosed with FMF than in the control group. (-18.0±2.0/-22.5±2.0; p<0.001).

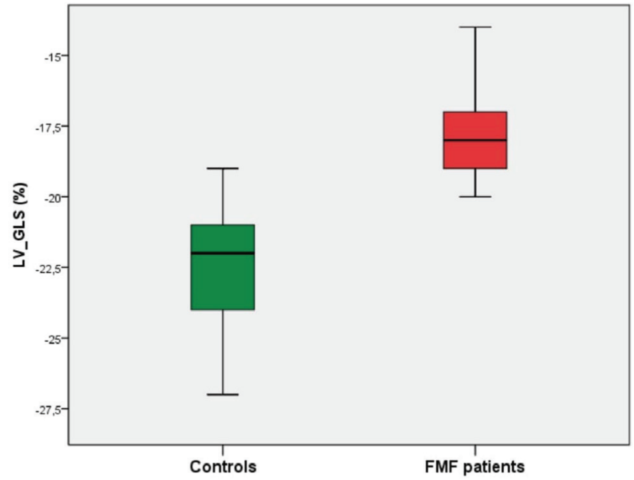


**Figure 1.** Comparison of LV-GLS values between individuals diagnosed with FMF and the control group
*LV-GLS: Left ventricular-global longitudinal strain, FMF: Familial Mediterranean Fever*

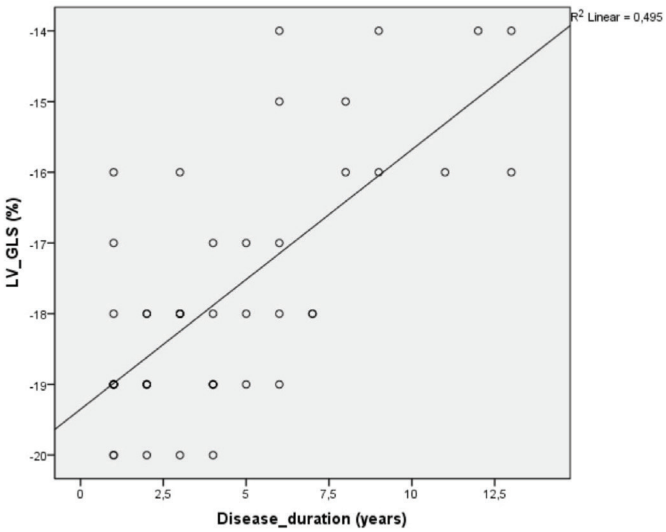


**Figure 2.** Relationship between disease duration and LV-GLS value in individuals diagnosed with FMF
*LV-GLS: Left ventricular-global longitudinal strain, FMF: Familial Mediterranean Fever*

**Table 2.** Features of conventional echocardiographic and two-dimensional speckle tracking longitudinal strain parameters of patients

| Number of patients (n) | FMF (n=50) | Controls (n=50) | p |
|---|---|---|---|
| LVEF (%) | 70.2±5.5 | 71.3±5.9 | 0.338 |
| LVEDD (cm) | 4.2±0.5 | 4.1±0.5 | 0.766 |
| LVESD (cm) | 2.4±0.2 | 2.5±0.3 | 0.399 |
| IVST (cm) | 0.8±0.2 | 0.7±0.2 | 0.775 |
| PWT (cm) | 0.7±0.1 | 0.7±0.2 | 0.781 |
| LA (cm) | 2.7±2.1 | 2.6±1.9 | 0.431 |
| Stroke volume (mL) | 55.2±19.5 | 53.4±18.7 | 0.573 |
| WMSI | 1.08±0.12 | 1.06±0.14 | 0.610 |
| E (cm/s) | 98.2±17.2 | 101.5±16.6 | 0.492 |
| A (cm/s) | 58.3±12.2 | 56.6±14.1 | 0.515 |
| E/A ratio | 1.6±0.2 | 1.7±0.1 | 0.488 |
| DT (ms) | 120.7 ±20.8 | 118.1±16.7 | 0.482 |
| IVRT (ms) | 57.1±14.3 | 52.8±15.8 | 0.163 |
| Lateral E’ (cm/s) | 13.2±2.2 | 12.7±2.0 | 0.265 |
| Lateral A’(cm/s) | 7.1±1.5 | 6.5±1.4 | 0.102 |
| E’/A’ | 1.9±0.4 | 1.9±0.5 | 0.571 |
| LV-GLS (%) | -18.0±2.0 | -22.5±2.0 | <0.001 |

*LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, IVST: Interventricular septum thickness, PWT: posterior wall thickness, LA: Left atrium, WMSI: Wall motion score index, DT: deceleration time, IVRT: Isovolumic relaxation time, LV-GLS: Left ventricular global longitudinal strain, E: Early diastole, A: Late diastole, n: Number*

2. A positive and statistically significant relationship was detected between the disease duration and LV-GLS values of individuals diagnosed with FMF ($r=0.608/p<0.001$).

Some publication reported that ejection fraction (EF) duration was lower in patients compared to controls and they suggested that FMF patients should undergo regular ECG investigations with conventional, strain and strain-rate techniques[8,18]. Contrastingly, other studies showed that there was no difference regarding EF between adult FMF patients and controls[19,20].

Previous studies have reported conflicting results on this matter. In our study, LVEF was not statistically significantly different between the groups. This can be explained due to the fact that the patients were children and the disease periods were short.

In a study, diastolic dysfunction was demonstrated in FMF patients by tissue Doppler imagining by ECG (TDE). In the same study, it was reported that mitral IVRT was prolonged while the mitral lateral annulus Em, Am, and Em/Am ratio were significantly reduced among FMF patients[20]. Kalkan et al.[21], similar to our study, performed strain measurements in addition to TDE in pediatric patients. The authors concluded that systolic strain and strain rate values were damaged in FMF patients, but they could not show the presence of cardiac involvement via the TDE method; the Sm, Em, Am, MPIm and mitral IVRT values were similar for patients and controls. The findings of our study were in contrast with the findings of Tavil et al.[20], but similar to the findings of Kalkan et al.[21].

To summarize, we did not observe any significant difference between the groups regarding TDE findings, while LGS value was found to be lower in the FMF patients.

A statistically significant positive correlation was found between disease duration and LV-GLS values of individuals diagnosed with FMF ($r=0.608/p<0.001$).

It shows that the longer it has had FMF disease, the more it has been subclinically affected by heart functions. Studies in adult FMF patients support this[18].

Kalkan et al.[21] also reported that LGS was significantly lower in FMF patients as well as Radial Global Strain, whereas circumferential global strain was similar.

We stated that this might be explained by the fact that the left ventricle endocardium suffered relatively more from adverse effects such as, hypoperfusion, fibrosis, and ischemic changes.

Cardiovascular magnetic resonance (CMR) is a reference standard for the diagnosis of cardiac amyloidosis and is also an excellent tool for risk stratification and disease tracking. It provides accurate measurement of the heart walls and is also useful for the identification of the myocardium. However, considerable experience is required for CMR interpretation. Motion artefacts are generally not present or feasible due to the presence of non-magnetic resonance compatible implantable devices. ECG is crucial for clinical suspicion and initial assessment of cardiac involvement. Amyloid infiltration leads to thickening of the ventricular walls (12 mm) in a concentric pattern due to the inability of the left ventricular cavity to expand. CMR was not applied in our study[22,23].

After the evaluation of all data, we concluded that reduction in global strain might be an important finding in the early diagnosis of cardiac diseases in pediatric FMF patients.

Our study group was relatively small and consisted of patients with a short disease period. A larger sample group and prospective studies are needed to confirm the results of our study.

## Conclusion

In this study, we evaluated 50 FMF children aged between 5 and 19 years and 50 healthy children with conventional ECG and GLS measurements were performed using 2D speckle tracking ECG. They observed no statistically significant relationship between sex and duration of illness. GLS values measured by two-dimensional speckle tracking between the groups were significantly lower in individuals diagnosed with FMF compared to the control group. They conclude speckle tracking ECG can provide the chance to reveal subclinical ventricular dysfunction before cardiac dysfunctions progress in children with FMF.

### Ethics

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of İstanbul University (decision no and date: 951 and 11.05.2015).

**Informed Consent:** Prospective study. All the patients gave approval.

**Peer-review:** Internally and externally peer-reviewed.

### Authorship Contributions

Concept: E.A., Design: E.A., F.M.K., G.D., Ö.K., R.E.Ö., Data Collection or Processing: E.A., F.M.K., G.D., Ö.K., Analysis or Interpretation: E.A., F.M.K., G.D., Literature Search: E.A., F.M.K., G.D., Ö.K., R.E.Ö., Writing: E.A., F.M.K.

**Conflict of Interest:** All the authors had no conflict of interest.

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# Association Between Coronary Artery Ostial Diameter Ratio and Stenotic Coronary Artery Disease in Patients Undergoing Elective Coronary Angiography

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## Abstract

**Objectives:** Besides the traditional cardiovascular risk factors, there are numerous anatomical and functional parameters that affect the coronary atherosclerosis and subsequent stenotic coronary artery disease (CAD). Previous studies reported a significant association between coronary artery diameter and stenotic CAD. However, no study has investigated the association between the ratio of ostial diameter of the main coronary arteries and stenotic CAD. We aimed to investigate whether coronary artery ostial diameter ratio (CAOD-R), which is calculated as dividing the left main coronary artery (LMCA) ostial diameter by the right coronary artery (RCA) ostial diameter, was associated with the presence of stenotic CAD in patients undergoing elective coronary angiography.

**Materials and Methods:** Four hundred and thirty-six patients who underwent elective coronary angiography were included in the study. CAOD-R was calculated from digital angiograms for all patients, and patients were divided into two groups as CAOD-R ≤ 1or >1. The groups were compared regarding the frequency of patients with stenotic CAD, and the association of CAOD-R with the presence of stenotic CAD was investigated.

**Results:** According to calculated CAOD-R, 142 (32.6%) patients were in the CAOD-R ≤1 group and 294 (67.4%) patients were in the CAOD-R >1 group. Patients with CAOD-R ≤1 had significantly higher frequency of stenotic CAD

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## Abstract

compared to patients with CAOD-R >1 (61.9% vs 41.1%, p<0.001). In the subgroup analysis of patients with stenotic CAD, while the frequency of left anterior descending (LAD) artery stenosis was significantly higher in the CAOD-R ≤1 patient group (46.6% vs 38.8%, p=0.006), the frequency of RCA stenosis was significantly higher in the CAOD-R >1 patient group (28.9% vs 18.2%, p=0.002). There were no differences between the groups regarding the frequency of stenotic lesions in LMCA and left circumflex artery. Furthermore, multivariate analysis demonstrated that CAOD-R was an independent predictor of stenotic CAD (Odds ratio: 0.824, 95% confidence interval: 0.721-0.947, p<0.001).

**Conclusion:** The present study demonstrated that CAOD-R was an independent predictor of stenotic CAD in patients undergoing elective coronary angiography. As an easily calculated parameter from angiographic images, CAOD-R may be useful in the further risk assessment of CAD patients undergoing elective coronary angiography.

**Keywords:** Coronary artery disease, coronary artery diameter, coronary angiography, coronary artery ostial diameter ratio

## Introduction

Atherosclerosis is a progressive disease that has a complex pathophysiology and generally manifests as narrowing of the arteries[1]. Coronary artery disease (CAD) is the life-threatening consequence of the atherosclerosis of the coronary vasculature, and despite the considerable improvements in the both diagnostic and therapeutic methods, it remains as a major reason for morbidity and mortality worldwide[2]. Chronic coronary syndrome (CCS), previously named as stable CAD, is the main manifestation of the coronary atherosclerosis and includes the majority of patients with CAD[3]. From inflammation to endothelial dysfunction, numerous factors play roles in the occurrence of CAD; however, traditional major cardiovascular risk factors such as age, male gender, smoking, hypercholesterolemia, hypertension and diabetes mellitus (DM) are considered as main triggers of both beginning and progression of the coronary atherosclerosis that leads CCS[3,4]. Nevertheless, CAD has a complex pathophysiology and mechanism, and interaction between clinical and anatomical parameters may take a role in the emergence or acceleration of coronary atherosclerosis, regardless of traditional cardiovascular risk factors[5].

Variations in the anatomy of the coronary vasculature, in particular coronary artery size may be associated with the occurrence of stenotic CAD, and previous reports indicated a significant inverse association between coronary artery diameter and CAD severity[6,7]. However, no study has investigated the relationship between ostial diameter ratio of the main coronary arteries and stenotic CAD. Therefore, in the present study, we aimed to investigate whether angiographically detected coronary artery ostial diameter ratio (CAOD-R), which is defined as dividing the ostial diameter of left main coronary artery (LMCA) to ostial diameter of right coronary artery (RCA), predicted stenotic CAD in the epicardial coronary arteries.

## Materials and Methods

### Study Population

The medical records of 451 consecutive CCS patients who underwent elective coronary angiography between January 2018 and June 2020 were retrospectively screened for the study. Among patients screened, 15 patients were excluded (11 patients for insufficient visualization of coronary artery ostium due to difficulties in the cannulation of coronary ostium and non-selective injection of the contrast media, three patients for ostial right coronary artery (RCA) lesion and one patient for ostial LMCA lesion) from the study. All in all, the remaining 436 patients were included in the study. As a part of routine examination, all patients underwent a cardiac and systemic physical examination. A detailed echocardiography was performed to all study participants and a surface 12-lead electrocardiography was obtained from patients. Laboratory analyses were made from venous blood samples after an overnight fasting. Hypertension was defined as systolic blood pressure levels of ≥140 mmHg and/or diastolic blood pressure levels of ≥90 mmHg and/or known treatment with antihypertensive medications. DM was defined as ≥2 fasting plasma glucose levels of ≥126 mg/dL, or 2-hour plasma glucose levels of ≥200 mg/dL, or glycated hemoglobin (HbA1c) levels of ≥6.5%, or documented treatment with antidiabetic drugs. Previous CAD was defined based on prior angiographic reports and/or documentation of myocardial ischemia on non-invasive tests, and smoking was defined as the regular use of cigarettes. The study protocol complied with the Declaration of Helsinki and approved by the local ethics committee (Gaziosmanpaşa University Medical School Clinical Trials Ethics Committee, on 25.06.2020 with project number 20-KAEK-150).

### Angiographic Findings and Coronary Artery Ostial Diameter Ratio

All patients underwent elective diagnostic coronary angiography in the presence of positive or suspected result of non-invasive tests. Coronary angiography was performed according to standard clinical protocols via the femoral or radial arteries. Degree of coronary stenosis and ostial diameters of coronary arteries were calculated from digital angiograms for all patients. Ostial diameter of LMCA was calculated in left anterior oblique (LAO) caudal or antero-posterior caudal views, and ostial diameter of RCA was calculated in LAO views. Ostial diameters were calculated manually from digital angiograms within 3 mm of each coronary ostium, respectively. CAOD-R was calculated by dividing the LMCA ostial diameter by the RCA ostial diameter. Figure 1 demonstrates the schematic illustration of the calculation of CAOD-R. Stenotic CAD was defined as ≥50% stenosis in any segments of the epicardial coronary arteries.

Patients were divided into two groups according to calculated CAOD-R ≤1 or >1. The groups were compared regarding the frequency of patients with stenotic CAD, and the association of CAOD-R with the presence of stenotic CAD was investigated.

### Statistical Analysis

Continuous variables were expressed as mean ± standard deviation whereas categorical variables were expressed as percentages. Normality distribution of continuous variables was tested with the Kolmogorov-Smirnov test. Student t-test was used to compare the normally distributed continuous variables, and categorical variables were compared with the chi-square test or Fisher's Exact test. To determine the independent predictors of stenotic CAD, a multivariate logistic regression analysis was performed. All variables with $p<0.05$ in univariate analysis were included in the model. A p-value of $<0.05$ was considered to indicate statistical significance.

## Results

According to calculated CAOD-R, 142 (32.6%) patients were assigned in the CAOD-R ≤1 group and 294 (67.4%) patients were assigned in the CAOD-R >1 group. The frequency of patients with DM was significantly higher in the CAOD-R ≤1 patient group compared to those with CAOD-R >1. Importantly, based on the angiographic results, patients with CAOD-R ≤1 had significantly higher frequency of stenotic CAD compared to patients with CAOD-R >1 (61.9% vs 41.1%, $p<0.001$). The groups were

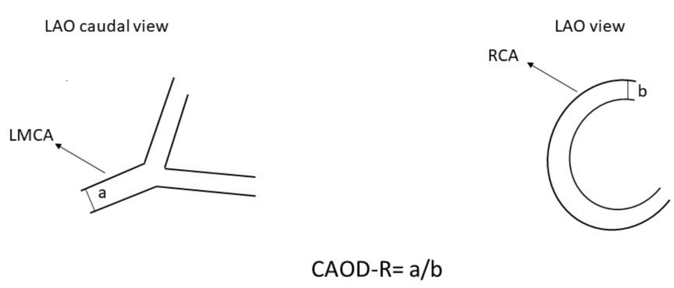


**Figure 1.** Schematic illustration of the calculation of coronary artery ostial diameter ratio
*LAO: Left anterior oblique, LMCA: Left main coronary artery, CAOD-R: Coronary artery ostial diameter ratio*

similar regarding the coronary dominance pattern. Table 1 demonstrates the clinical, laboratory and angiographic characteristics of patients according to CAOD-R.

When comparing the patients with and without stenotic CAD, patients with stenotic CAD were older, and the frequency of male gender, DM and dyslipidemia were significantly higher in patients with stenotic CAD compared to those without stenotic CAD. Clinical characteristics of patients with and without stenotic CAD are presented in Table 2. In the subgroup analysis of patients with stenotic CAD, while the frequency of left anterior descending (LAD) artery stenosis was significantly higher in the CAOD-R ≤1 patient group (46.6% vs 38.8%, p=0.006), the frequency of RCA stenosis was significantly higher in the CAOD-R >1 patient group (28.9% vs 18.2%, p=0.002). There were no differences between the groups regarding the frequency of stenotic lesions in LMCA and left circumflex artery. Table 3 shows the distribution of stenotic lesions in epicardial coronary arteries according to CAOD-R.

Furthermore, multivariate logistic regression analysis demonstrated that CAOD-R was an independent predictor of the presence of stenotic CAD (odds ratio: 0.824, 95% confidence interval: 0.721-0.947, p<0.001). Table 4 demonstrates the independent predictors of stenotic CAD in multivariate analysis.

**Table 1.** Clinical, laboratory and angiographic characteristics of patients according to coronary artery ostial diameter ratio

| | CAOD-R ≤1 (n=142) | CAOD-R >1 (n=294) | p |
|---|---|---|---|
| Age (years) | 51.4±12.7 | 52.2±13.5 | 0.274 |
| Sex, male, n (%) | 91 (64.1%) | 193 (65.6%) | 0.114 |
| Hypertension, n (%) | 53 (37.3%) | 108 (36.7%) | 0.374 |
| Diabetes mellitus, n (%) | 41 (28.9%) | 64 (21.8%) | 0.025 |
| Smoking n (%) | 37 (26.1%) | 85 (28.9%) | 0.475 |
| Previous CAD, n (%) | 30 (21.1%) | 67 (22.7%) | 0.817 |
| LVEF (%) | 58.7±8.4 | 56.8±9.1 | 0.248 |
| Radial angiography n, (%) | 26 (18.3%) | 51 (17.3%) | 0.879 |
| WBC count (×10$^3$/μL) | 8.1±1.4 | 7.9±1.3 | 0.170 |
| Platelet count (×10$^3$/μL) | 255±55 | 261±59 | 0.408 |
| Hemoglobin (g/dL) | 12.2±1.7 | 13.1±1.8 | 0.044 |
| Creatinine (mg/dL) | 0.9±0.15 | 0.9±0.13 | 0.974 |
| ALT (U/L) | 23.5±9.4 | 22.2±8.2 | 0.571 |
| Total cholesterol (mg/dL) | 183±40.5 | 180±42.7 | 0.344 |
| LDL-cholesterol (mg/dL) | 107.2±35.4 | 97.9±32.4 | 0.005 |
| HDL-cholesterol (mg/dL) | 40.3±8.8 | 41.2±7.9 | 0.082 |
| Right dominance n, (%) | 111 (78.2%) | 214 (72.8%) | 0.378 |
| Stenotic CAD, n, (%) | 88 (61.9%) | 121 (41.1%) | <0.001 |

*CAOD-R: Coronary artery ostial diameter ratio, CAD: Coronary artery disease, LVEF: Left ventricular ejection fraction, WBC: White blood cell, ALT: Alanine aminotransferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, n: Number*

**Table 2.** Comparison of the clinical characteristics of patients according to the presence or absence of stenotic CAD

| | Stenotic CAD (+) (n=209) | Stenotic CAD (-) (n=227) | p |
|---|---|---|---|
| Age (years) | 55.6±14.1 | 50.5±13.8 | 0.022 |
| Sex, male, n (%) | 158 (75.6%) | 126 (55.5%) | <0.001 |
| Hypertension, n (%) | 85 (40.7%) | 76 (33.5%) | 0.078 |
| Diabetes mellitus, n (%) | 81 (38.7%) | 24 (10.6%) | <0.001 |
| Smoking n (%) | 67 (32.1%) | 55 (24.2%) | 0.006 |
| Previous CAD, n (%) | 51 (24.4%) | 46 (20.2%) | 0.441 |
| LVEF (%) | 57.2±9.4 | 57.8±8.9 | 0.916 |
| WBC count (×10$^3$/μL) | 7.9±1.4 | 8.0±1.5 | 0.295 |
| Platelet count (×10$^3$/μL) | 261±58 | 257±61 | 0.108 |
| Hemoglobin (g/dL) | 12.6±1.8 | 12.8±1.8 | 0.571 |
| Creatinine (mg/dL) | 0.9±0.1 | 0.9±0.1 | 0.881 |
| ALT (U/L) | 22.3±10.2 | 22.9±9.7 | 0.772 |
| Total cholesterol (mg/dL) | 188±49.5 | 175±47.6 | 0.044 |
| LDL-cholesterol (mg/dL) | 108.1±32.2 | 94.2±29.6 | <0.001 |
| HDL-cholesterol (mg/dL) | 40.6±8.4 | 41.2±7.2 | 0.227 |

*CAD: Coronary artery disease, LVEF: Left ventricular ejection fraction, WBC: White blood cell, ALT: Alanine aminotransferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, n: Number*

**Table 3.** Distribution of stenotic lesions in epicardial coronary arteries according to coronary artery ostial diameter ratio

| Vessel | CAOD-R ≤1 (n=88 stenotic lesions) | CAOD-R >1 (n=121 stenotic lesions) | p |
|---|---|---|---|
| LMCA, n (%) | 4 (4.5%) | 5 (4.1%) | 0.984 |
| LAD, n (%) | 41 (46.6%) | 47 (38.8%) | 0.006 |
| LCX, n (%) | 27 (30.7%) | 34 (28.1%) | 0.241 |
| RCA, n (%) | 16 (18.2%) | 35 (28.9%) | 0.002 |

*CAOD-R: Coronary artery ostial diameter ratio, LMCA: Left main coronary artery, LAD: Left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery, n: Number*

**Table 4.** Independent predictors of stenotic CAD in multivariate analysis

| Variable | Odds ratio | %95 Confidence Interval | p |
|---|---|---|---|
| CAOD-R | 0.824 | 0.721-0.947 | <0.001 |
| LDL-cholesterol | 1.221 | 1.151-1.914 | <0.001 |
| Male, gender | 1.542 | 1.225-2.106 | <0.001 |
| Diabetes mellitus | 2.134 | 1.474-3.261 | <0.001 |

*CAD: Coronary artery disease, CAOD-R: Coronary artery ostial diameter ratio, LDL: Low-density lipoprotein, n: Number*

## Discussion

The main finding of our study was that the frequency of stenotic CAD was significantly higher in patients with CAOD-R ≤1 compared to patients with CAOD-R >1. In addition, CAOD-R was found to be an independent predictor of stenotic CAD in CCS patients undergoing elective coronary angiography. Also, CAOD-R ≤1 was found to be associated with more frequent LAD artery stenosis and CAOD-R >1 was found to be associated with more frequent RCA stenosis. To our knowledge, this is the first study investigating the association of CAOD-R with stenotic CAD in CCS patients.

CAD is characterized by atherosclerotic plaques in the epicardial coronary arteries and coronary angiography is the gold standard diagnostic method for the diagnosis of stenotic coronary atherosclerotic lesions(8). Age, gender, increased blood pressure, DM, obesity and dyslipidemia are well-known traditional risk factors in all stages of CAD from its beginning to symptomatic obstructive CAD; however, there may be numerous other risk factors for coronary atherosclerosis due the dynamic nature and the complex pathophysiology of CAD(1,3,9). In this sense, anatomic variations in the coronary vascular tree have also been investigated as a risk factor for coronary atherosclerosis and stenotic CAD, and some studies reported a significant association between coronary anatomy and CAD severity(5,10). Moreover, previous studies reported a significant inverse association between coronary artery size and atherosclerotic cardiovascular disease and reported higher frequency of stenotic CAD in small caliber vessels(6,7,11). These findings point out an important link between coronary artery diameter and coronary atherosclerosis, in particular, for stenotic CAD. Considering the pathophysiology of the coronary atherosclerosis, it is sensible to consider that small caliber vessels require smaller plaque burden for stenotic lesions. Also, it has been demonstrated that variations in the size of the coronary arteries may influence the coronary blood flow distribution in the coronary arterial tree that may affect the myocardial perfusion and atherosclerosis(12). Therefore, it seems reasonable to investigate the role of the anatomy of the coronary vasculature in the pathophysiology of the coronary atherosclerosis and stenotic CAD. Nevertheless, these studies generally focused on only diseased vessel diameter and no study has investigated the importance of the ostial diameter of LMCA and RCA. In the present study, we defined a novel parameter named as CAOD-R and demonstrated a significant association between CAOD-R and the presence of stenotic CAD in CCS patients undergoing elective coronary angiography. We found an inverse relationship between CAOD-R and the presence of stenotic CAD, which indicates the importance of ostial size of the main coronary arteries in the distribution of coronary blood flow and severity of coronary atherosclerosis. Besides the predictive value of CAOD-R for stenotic CAD, we also demonstrated that CAOD-R ≤1 was significantly associated with stenotic lesions in LAD artery, and CAOD-R >1 was significantly associated with stenotic lesions in RCA. Therefore, CAOD-R may be useful in the prediction of stenotic lesions in different coronary arteries according to its calculated ratio. The findings of the present article are in consistent with the previously published data and provide a novel finding that indicates the clinical importance of diameter ratio of the main coronary arteries for predicting stenotic CAD in the different segments of the coronary vascular tree.

### Study Limitations

The present study has some limitations. First, the size of the each coronary artery was not calculated; however, it should be noted that the association between coronary artery size and stenotic CAD has been previously demonstrated. Second, the present study included the patients undergoing elective coronary angiography, and hence the association of CAOD-R with an acute coronary event was not investigated, which may be a topic for another study. Finally, although we considered both traditional and non-traditional cardiovascular risk factors, there may be still some other factors affecting coronary atherosclerosis due to its complex pathophysiology.

## Conclusion

Ostial size of the main coronary arteries may significantly affect the coronary blood flow distribution and coronary hemodynamics that may play a role in the coronary atherosclerosis. In the present study, we demonstrated that as a novel parameter, "CAOD-R" was an independent predictor of stenotic CAD in CCS patients undergoing elective coronary angiography. Additionally, CAOD-R may also be useful in the predicting LAD or RCA stenosis according to its calculated value. Therefore, as an easily calculated parameter from angiographic images, CAOD-R may be useful in the further risk assessment of patients undergoing elective coronary angiography.

### Ethics

**Ethics Committee Approval:** The study was approved by Gaziosmanpaşa University Medical School Clinical Trials Ethics Committee on 25.06.2020 with project number 20-KAEK-150.

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: M.E., C.E., Design: M.E., C.E., Data Collection or Processing: M.E., C.E., Analysis or Interpretation: M.E., C.E., Literature Search: M.E., C.E., Writing: M.E., C.E.

**Conflict of Interest:** The authors have no commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest.

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# The Relationship Between Endothelial Functions and HDL/LDL Ratios in Patients with Coronary Artery Disease

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## Abstract

**Objectives:** Endothelial dysfunction plays an important role in the initial stage of atherosclerosis, the growth of atherosclerotic plaque and the development of thrombogenic events. Low-density lipoprotein (LDL) cholesterol levels are associated with the risk of cardiovascular disease. It also inhibits endothelium-dependent vasodilation by disrupting the activity of nitric oxide (NO) synthase and causes endothelial dysfunction. It has been shown that high-density lipoprotein (HDL) cholesterol increases the production of NO and endothelial NO synthase that causes vascular dilatation directly or indirectly, and also supports endothelial cell migration and proliferation through different mechanisms. In our study, we aimed to investigate the relationship between HDL/LDL ratios and endothelial functions in patients with coronary artery disease (CAD) documented through coronary angiography (CAG).

**Materials and Methods:** Fifty-seven patients with CAD documented through CAG were included in the study. Endothelial functions were evaluated with the flow mediated vasodilation (FMD) test, which is the most commonly used non-invasive method for endothelial function assessment. In statistical analysis, the change in arterial diameter was examined by the paired sample t-test.

**Results:** The average age of 57 patients included in the study was 61.1±10.1 years and 70% of these patients were male and 30% were female. The mean body mass index was 27.8±5.7 kg/m$^2$ and 57.9% of the patients were NYHA class I. In the FMD test, the mean radial artery percentage diameter change was found to be 12.61% (±3.62). The average HDL/LDL ratio of the patients included in the study was 0.53 (±0.26), and the median value was 0.42 (minimum 0.27 - maximum 1.50). There was a weak positive correlation between HDL/LDL ratios and FMD percentage change (r =+0.379, p=0.04).

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## Abstract

**Conclusion:** As HDL/LDL ratios increase in patients with CAD, the percentage change of flow-mediated dilatation, which is an indicator of endothelial functions, also increases.

**Keywords:** Coronary artery disease, endothelial dysfunction, HDL cholesterol, LDL cholesterol

## Introduction

The endothelium is the largest organ of our body, which is located in the vascular system and plays an important role in the protection of vascular hemostasis in many physiological and pathological events[1-4]. The endothelium is a dynamic organ that can synthesize and release vasoconstrictor and vasodilator substances. When endothelial dysfunction occurs, the synthesis of factors such as nitric oxide (NO), which causes vasodilation, is impaired[5]. Endothelial dysfunction plays an important role in the initial stage of atherosclerosis, atherosclerotic plaque growth, and development of thrombogenic events[6]. Low-density lipoprotein (LDL) cholesterol levels are associated with the risk of cardiovascular disease and increase susceptibility to complications of atherosclerosis[7]. Oxidized LDL inhibits endothelium-dependent vasodilation by disrupting the activity of NO synthase and causes endothelial dysfunction[8]. High density lipoprotein (HDL) has been shown to increase the production of NO and endothelial NO synthase causing vascular dilatation directly and indirectly, and it has been shown to support endothelial cell migration and proliferation through different mechanisms[9-11]. Literature information on the effects of HDL and LDL levels on vascular endothelial functions in patients with coronary artery disease (CAD) is partially insufficient. Therefore, in our study, we aimed to investigate the relationship between HDL/LDL ratios and endothelial functions in patients with CAD documented through coronary angiography (CAG).

## Materials and Methods

Fifty-seven patients between the ages of 18 and 80 years, who had CAD documented through CAG, were included in the study. Patients who could not have a pulse from the radial artery, who could not have an optimal ultrasonographic evaluation, and who did not give informed consent were excluded from the study. In addition, patients with acute coronary syndrome and patients with normal coronary artery patency as a result of CAG were excluded from the analysis. Our study is a prospective, observational study. The clinical data of the patients were filled in the relevant places in the case report form. The medical treatment of the patients included in the study was arranged by the attending physician, and all patients were under optimal medical treatment in terms of CAD. Ethics committee approval of our study was obtained from Ege University Faculty of Medicine Clinical Research Ethics Committee on 26.12.2017 with the decision number 17-12.1/22. Written informed consent was obtained from all participants.

### Flow Mediated Vasodilation Test

Endothelial functions were evaluated by using the flow mediated vasodilation (FMD) test. GE Healthcare Vivid E9 4D Cardiovascular Ultrasound System Device, 11L-D, 4.5-12 MHz probe was used for this test. The environment where the FMD test applied was quiet, at room temperature and bright. The FMD test was performed after eight hours of fasting, and patients had not consumed products such as caffeine, cigarettes, or tea that could affect the procedure. In FMD test, the arm cuff inflation till 220 mmHg lasted for 5 minutes for the occlusion of the distal hand or distal forearm arteries. Then, the cuff was deflation. As a result, endothelial factors such as NO was released, causing vasodilation in response to reactive hyperemia in distal and proximal vascular beds were provided. In order to measure the maximum artery diameter, the arterial diameter change was recorded by ultrasonographic method for 3 minutes after the cuff was deflated.

FMD percentage change was made by calculating the following formula;

$$FMD = (\%) \frac{(\text{Diameter after reactive hyperemia} - \text{Basal Arterial Diameter})}{\text{Basal Arterial Diameter}}$$

The radial artery diameter was measured in centimeters (cm) from the anterior wall intima to the posterior wall intima. Arterial diameter measurements were taken at the end of the diastole by determining the cardiac cycle with electrocardiography. The diameter and percentage change of the radial artery at baseline and after FMD were recorded.

### Statistical Analysis

IBM SPSS Statistics 25.0 Program was used. The suitability of numerical variables to normal distribution was examined by using the Kolmogorv-Smirnov ($n \geq 50$) and Shapiro-Wilk ($n<50$) tests. Numerical variables were given as mean and standard deviation or median (minimum-maximum). Categorical variables were given as numbers and percentages. The Mann-Whitney U test was used because it was not suitable for normal distribution. The change in arterial diameter was examined with the paired sample t-test. The relationship between numerical variables was analyzed by using the Spearman correlation analysis. The significance level was accepted as <0.05 for all hypotheses.

## Results

While the average age of 57 patients included in the study was 61.1±10.1 years, 70% of the patients were male and 30% were female. The mean body mass index was 27.8±5.7 kg/m$^2$ and 57.9% of the patients were New York Heart Association (NYHA) class I, 42.1% were NYHA class II. The most common complaints of the patients were chest pain at a rate of 50.9% and dyspnea at a rate of 35.1%. The complaint of palpitations was present in 8.8% of the patients. 29.8% of the patients had a history of smoking and 19.3% had a history of alcohol use. The demographic characteristics of the study population are summarized in Table 1. Hypertension was the most common comorbid disease in 78.9% of patients. Apart from hypertension, the most common comorbidities were diabetes at a rate of 38.6% and hyperlipidemia at a rate of 33.3%, respectively. Five patients (8.8%) had chronic obstructive pulmonary disease and four patients (7%) had chronic kidney disease. Comorbid conditions of the patients included in the study are summarized in Table 2. Among the biochemical parameters, the mean urea value was 34.88 (±18.58), the mean HDL value was 44.88 (±10.86) mg/dL, the LDL value was 96.86 (±35.90) mg/dL, the mean hemoglobin value was 13.52 (±2.25) g/dL, and the mean fasting glucose value was 131.84 (±61.11) mg/dL. In echocardiography, the mean left ventricular ejection fraction value was 53.5±9.3%, the mean LV end-diastolic diameter was 4.87 (±0.56) cm, and the left atrium (LA) diameter was 3.9±0.6 cm. Laboratory and imaging findings of the patients are summarized in Table 3.

In the FMD test, the highest artery diameter was taken as basis in the measurements made during 3 minutes after hyperemia. The mean radial artery basal diameter was 0.25 (±0.029) cm, and the mean radial artery diameter after FMD was 0.28 (±0.033) cm ($p<0.001$). The mean

**Table 1.** Demographic characteristics of the study population

| Demographic features | (n=57) |
|---|---|
| Age, year | 61.1±10.1 |
| Male sex, n (%) | 40 (70.1) |
| BMI (kg/m$^2$) | 27.8±5.7 |
| Systolic BP, mmHg | 143.0±19.7 |
| Diastolic BP, mmHg | 79.7±13.6 |
| Heart rate/min | 76.4±13.6 |
| NYHA Class I, n (%) | 33 (57.9) |
| NYHA Class II, n (%) | 24 (42.1) |
| Chest pain, n (%) | 29 (50.9) |
| Dyspnea, n (%) | 20 (35.1) |
| Palpitation, n (%) | 5 (8.8) |
| Smoking, n (%) | 17 (29.8) |
| Alcohol use, n (%) | 11 (19.3) |

*BP: Blood pressure, NYHA: New York Heart Association, BMI: Body mass index, n: Number* radial artery percentage diameter change after FMD was 12.61% (±3.62). FMD test findings are summarized in Table 4, and the radial artery diameter change graph is shown in Figure 1.

The average HDL/LDL ratio of the patients included in the study was 0.53 (±0.26) and the median value was 0.42 (minimum 0.27 - maximum 1.50). There was a weak positive correlation between HDL/LDL ratios and the artery diameter percentage change that is showed as endothelial functions in FMD test (r =+0.379, p=0.04). The relationship between HDL/LDL ratios and FMD percentage change is shown in Figure 2.

**Table 2.** Comorbid diseases in study population

| Comorbid diseases | (n=57) |
|---|---|
| Hypertension, n (%) | 45 (78.9) |
| Diabetes mellitus, n (%) | 22 (38.6) |
| Hyperlipidemia, n (%) | 19 (33.3) |
| AF, n (%) | 2 (3.5) |
| COPD, n (%) | 5 (8.8) |
| Anemia, n (%) | 6 (10.5) |
| Chronic HF, n (%) | 4 (7) |
| CKD, n (%) | 4 (7) |
| Thyroid disease, n (%) | 3 (5.3) |

*AF: Atrial fibrillation, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, HF: Heart failure, n: Number*

**Table 3.** Laboratory and imaging findings of the patients

| Parameter | Mean (± standard deviation) |
|---|---|
| Urea, mg/dL | 34.88 (±18.58) |
| Creatinine, mg/dL | 1.06 (±0.84) |
| Total cholesterol, mg/dL | 169.68 (±41.03) |
| HDL, mg/dL | 44.88 (±10.86) |
| LDL, mg/dL | 96.86 (±35.90) |
| HDL/LDL ratio | 0.53 (±0.26) |
| WBC, k/mm$^3$ | 8.45 (±2.59) |
| Hemoglobin, g/dL | 13.52 (±2.25) |
| Fasting glucose, mg/dL | 131.84(±61.11) |
| TSH, mU/L | 2.05 (±1.49) |
| Ca, mg/dL | 9.45 (±0.67) |
| LVEF, % | 53.5 (±9.3) |
| LVEDD, cm | 4.87 (± 0.56) |
| LA, cm | 3.9 (±0.6) |
| Ascending aorta, cm | 3.60 (±0.49) |
| IVSD, cm | 1.1 (±0.2) |

*Ca: Calcium, HDL: High density lipoprotein, LDL: Low density lipoprotein, Mg: Magnesium, P: Phosphate, TSH: Thyroid stimulating hormone, LVEF: Left ventricular ejection fraction, LA: Left atrium, IVSD: Interventricular septum diastole, WBC: White blood cell*

## Discussion

Atherosclerosis is a multifactorial disease caused by inflammatory, immunological and genetic events[6]. Endothelial dysfunction is one of the main mechanisms in atherosclerotic process. Endothelial dysfunction not

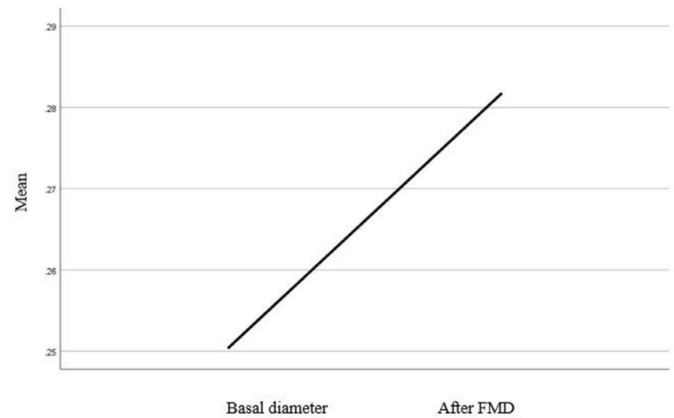


**Figure 1.** Radial artery diameter change graph in flow mediated vasodilation test
*FMD: Flow mediated vasodilation*

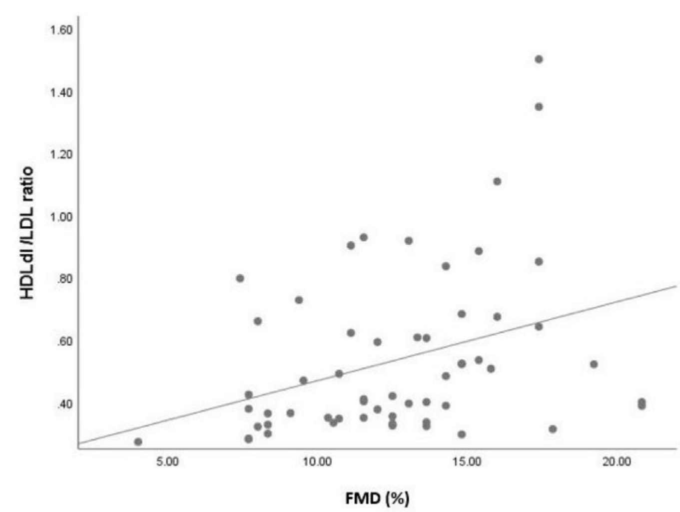


**Figure 2.** Relationship between HDL/LDL ratios and FMD percentage diameter change
*HDL: High density lipoprotein, LDL: Low density lipoprotein, FMD: Flow mediated vasodilation*

Table 4. Arterial diameter and percentage change in flow mediated vasodilation test

| FMD test | Basal diameter | Diameter after FMD | Percentage diameter change after FMD | p value |
|---|---|---|---|---|
| Mean (± standard deviation), cm | 0.25 (±0.029) | 0.28 (±0.033) | 12.61 (±3.62) | <0.001 |

*FMD: Flow mediated vasodilation*

only plays a role in the first step of the atherosclerotic process that causes plaque formation, but also causes plaque to grow, cracking the plaque and trigger thrombogenic events[12]. The endothelium produces NO, which inhibits the cellular pathways of inflammation, proliferation, and thrombosis[13,14]. In normal endothelium, acetylcholine causes vasodilation and increases blood flow by stimulating NO release, while in the presence of endothelial dysfunction, it directly stimulates vascular smooth muscle cells and leads to vasoconstriction[1,13,14].

Vascular endothelial cell is the main target of pathological or mechanical injury caused by some risk factors such as smoking, increased systolic blood pressure, high total cholesterol, and low HDL cholesterol level[15]. It has been observed that normal HDL taken from healthy subjects exhibits direct anti-atherogenic effects by modulating vascular endothelial functions[16-18]. HDL stimulates endothelial NO production by activating endothelial NO synthase (eNOS), and also has antioxidant, anti-inflammatory and antithrombotic effects[19-22]. We planned our study to evaluate the effect of HDL/LDL ratios on endothelial functions in patients with CAD under the same antithrombotic and anticoagulant treatment regimen.

Epidemiological studies have shown that HDL cholesterol has a protective effect against atherosclerosis, but the mechanism is not known exactly[23,24]. Experimental animal studies have shown that HDL infusion acutely improves endothelial function[25,26]. *In vitro*, HDL has been shown to protect endothelial cells against the damaging effects of LDL and to prevent oxidative modification of LDL particles[27].

The effects of HDL/LDL concentration ratios on vascular endothelial function in healthy individuals were evaluated on the basis of flow-mediated vasodilation response, which is a marker of endothelial function, and in our study, we found a weak positive correlation between HDL/LDL ratios and endothelial function.

In a study involving 26 patients who underwent routine diagnostic cardiac catheterization, it was found that high HDL levels improved intimal vasoconstriction in coronary arteries regardless of atherosclerotic wall thickness[28]. Plasma HDL cholesterol concentration is a strong independent predictor of NO-induced peripheral vasodilation in patients with hyperlipidemia, diabetes mellitus, and CAD[29-31]. As in animals, in individuals with hypercholesterolemia or low HDL, intravenous infusion of soluble HDL has been shown to improve the endothelium-dependent peripheral vasodilation by increasing NO bioavailability[32,33]. Oxidized LDLs are a potent inducer of endothelial dysfunction. The protective effects of HDL on endothelial function are very important due to its capacity to resist the destructive effects of oxidized LDL[17,34]. Low plasma HDL concentration is an independent predictor of endothelial dysfunction in healthy individuals and atherosclerotic patients[10]. Our study confirms this information, and our study demonstrated that as HDL/LDL ratio increased, flow-mediated dilatation which evaluates endothelial function non-invasively, also increased.

## Study Limitations

The single-center nature of our study is one of the limitations. The low number of patients may have reduced the power of the study. We believe that the strength of the weak correlation between HDL/LDL ratio and endothelial functions would increase if there were a higher number of patients. Another limitation of our study may be that endothelial functions were not evaluated by nitroglycerine mediated vasodilation test. The high ratio of male gender in the study may prevent the generalization of the study results over the population.

## Conclusion

HDL/LDL ratio is related to endothelial functions in patients with CAD. As the HDL/LDL ratio increases, flow-mediated dilatation increases. We think that this study will be a pioneer to randomized studies that will be conducted on parameters affecting endothelial functions in patients with CAD.

### Ethics

**Ethics Committee Approval:** Ethics committee approval of our study was obtained from EGE University Faculty of Medicine Clinical Research Ethics Committee on 26.12.2017 with the decision number 17-12.1/22.

**Informed Consent:** A signed informed consent form was obtained from the patients included in this study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.K., M.A., Concept: E.S., M.A., Design: M.K., E.S., Data Collection or Processing: M.K., Analysis or Interpretation: M.K., E.S., Literature Search: M.K., M.A., Writing: M.K., E.S.

**Conflict of Interest:** The authors declared that there was no conflict of interest related to this article.

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# Delayed Coronary Occlusion After Transcatheter Aortic Valve Replacement in an Elderly Patient with Atrial Fibrillation

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## Abstract

Transcatheter aortic valve replacement (TAVR) is an effective procedure in selected patients with symptomatic severe aortic stenosis. However, the complications associated with TAVR are still an important problem today. One of the life-threatening complications associated with TAVR is coronary occlusion, which requires immediate diagnosis and intervention. This serious complication also leads to poor prognosis and mortality. In this case, we aimed to present the late coronary artery occlusion due to thrombus after TAVR and to emphasize the uncertainties and complexities in antithrombotic treatment in patients with TAVR, which may lead to catastrophic outcomes, especially in patients with atrial fibrillation.

**Keywords:** Coronary occlusion, myocardial infarction, transcatheter aortic valve replacement

## Introduction

Aortic stenosis (AS) is a valvular heart disease that affects 5% of the elderly population[1]. Transcatheter aortic valve replacement (TAVR) has become the gold standard treatment option for patients with severe symptomatic AS and high or moderate risk for surgical aortic valve replacement[2]. Although the results of the TAVR procedure are positive over time and the complications decrease, the risk of life-threatening complications still remains. One of these is coronary occlusion (CO), which can have

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fatal consequences and is usually seen in the acute phase immediately after valve insertion. However, several cases of delayed coronary occlusion (DCO) have also been reported recently[3,4]. Therefore, we aimed to discuss an AF patient who was admitted to emergency department with acute myocardial infarction due to CO in the late period after TAVR procedure in this case report.

## Case Report

An 84-year-old female patient was admitted to the cardiology outpatient clinic with recurrent syncope attacks. She was under treatment with Dabigatran 110 mg 2x1 for AF and had no any documented cardiovascular diseases or cardiovascular risk factors such as hypertension and diabetes mellitus (DM). Her resting ECG showed normal ventricular responsive AF and left bundle branch block morphology. In the transthoracic echocardiography (TTE), aortic valve area was 0.82 cm$^2$, aortic velocity was 5.2 m/s and transaortic mean gradient was 52 mmHg. The left ventricular ejection fraction (LVEF) was measured as 55% by biplanar Simpson method and there was no wall motion abnormality. In addition, she underwent neurological evaluation and magnetic resonance imaging was performed due to recurrent syncope attacks. After the exclusion of cerebrovascular disease, TAVR procedure was planned because of the high surgical risk calculated by EuroSCORE method (27.3%). Coronary computed tomography (CT) angiography demonstrated the coronary ostium height as 18.5 mm, the sinus of valsalva diameter as 30.5 mm, and the sinotubular junction as 33 mm. On coronary CT angiographic images, the left main coronary artery (LMCA) and left anterior descending (LAD) coronary artery were normal, there was no significant lesion (<50%) in the right coronary artery (RCA) and there were plaque formations in the circumflex coronary artery (Cx) (Figure 1). Due to the absence of significant lesion, the invasive coronary angiography was not planned and the 29 mm-Medtronic Core Valve was implanted successfully via the right transfemoral route (Figure 2). After implantation, the dabigatran 110 mg 2x1 was switched to edoxaban 60 mg due to ease of use of single-dose and positive outcomes of ENGAGE AF-TIMI 48 trial[5] (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-

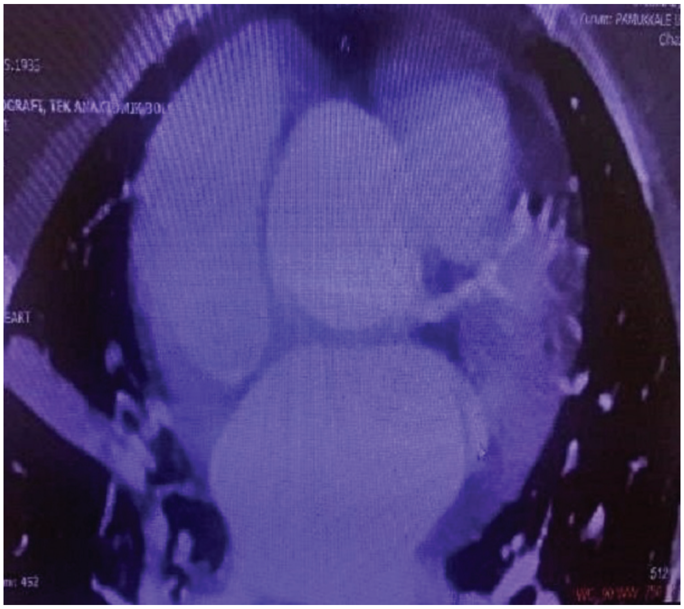

**Figure 1.** Imaging of the left main coronary artery (LMCA), left anterior descending artery (LAD) and Circumflex artery (Cx) in CT coronary angiography before TAVR procedure

*CT: Computed tomography, TAVR: Transcatheter aortic valve replacement*

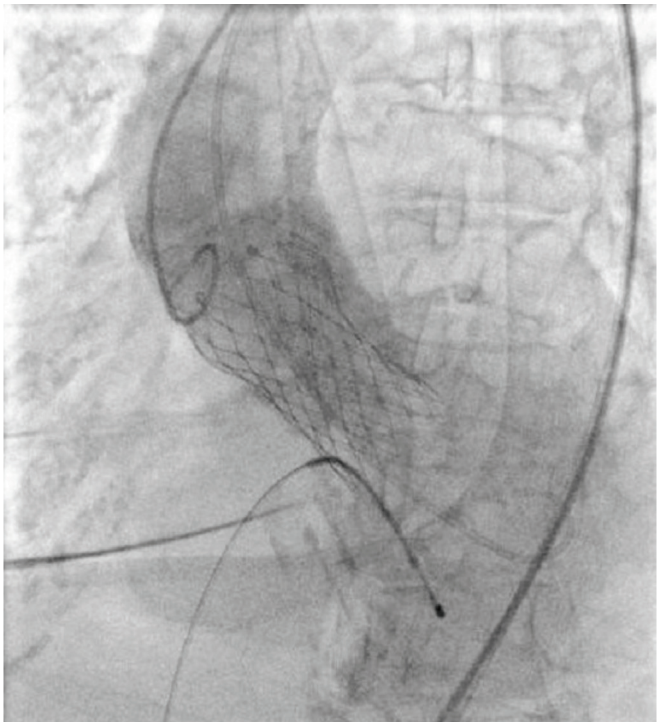

**Figure 2.** Angiographic view of the bioprosthetic aortic valve

Thrombolysis in Myocardial Infarction 48) in subgroup analysis of AF patients with TAVR. She was followed up with dual antithrombotic therapy consisting of 60 mg edoxaban and 75 mg clopidogrel after discharge. After three months of dual antithrombotic treatment, clopidogrel was stopped and continued with only edoxaban. No complication was reported, such as bleeding or thromboembolism during the first six months of follow-up. In serial TTE imagings, the mean transaortic valve gradient was 10 mmHg and aortic velocity was 1.4 m/s and there was no paravalvular leakage in bioprosthetic valve. However, in eight months after implantation, she was admitted to the emergency department in the third hour of chest pain. Her family reported that she had taken oral anticoagulants regularly and she had recurrent angina attacks for the last 3 days. At admission, peripheral pulses were weak and her blood pressure was 60/40 mmHg. EKG showed diffuse ST elevation in anterior leads with reciprocal changes in inferior leads (Figure 3). In bedside echocardiography, there was no problem in the bioprosthetic valve but the LVEF was 40% with hypokinesia at the anterior wall and septum. Clopidogrel 300 mg, acetylsalicylic acid (aspirin) 300 mg were given in the emergency department. She underwent cardiac catheterization by positive inotropic support due to hemodynamic deterioration and the door-to-balloon time was nearly 25-30 minutes. Coronary angiography showed the total occlusion of the ostium of LMCA with thrombus and percutaneous coronary intervention (PCI) was planned (Figure 4). Before the balloon angioplasty of Cx artery and LAD artery, intravenous 5000 IU of unfractionated heparin was used and three drug-eluting stents were implanted into LAD artery. However, the Thrombolysis in Myocardial Infarction (TIMI) flow grade III could not be supplied (Figure 5). She developed cardiac arrest one hour after cardiac catheterization. Unfortunately, she did not restore life by cardiopulmonary resuscitation and passed away.

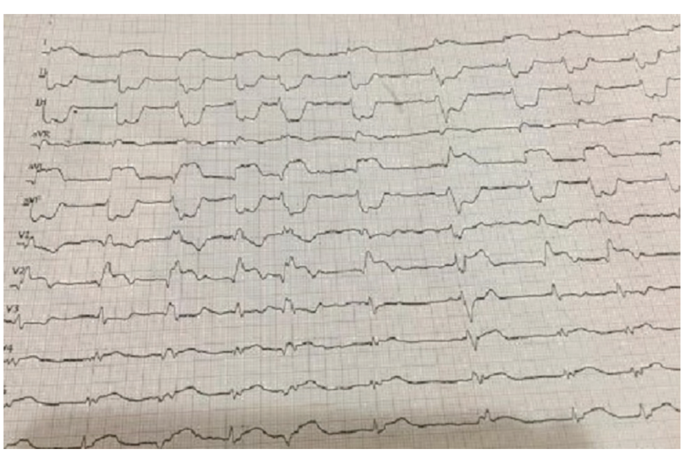

**Figure 3.** Diffuse ST elevation in anterior leads and reciprocal changes in inferior leads on ECG due to coronary occlusion

## Discussion

The TAVR procedure has become common in patients who are not suitable for surgical procedures in severe AS. However, this procedure is still associated with complications such as conduction defects, vascular complications, thromboembolic events and paravalvular leakage. CO after TAVR procedure is a rare life-threatening complication and was was described by Webb et al's study[6]. CO is more common in LMCA than RCA due to the higher localization of the right coronary ostium[7]. This complication usually develops acutely after the

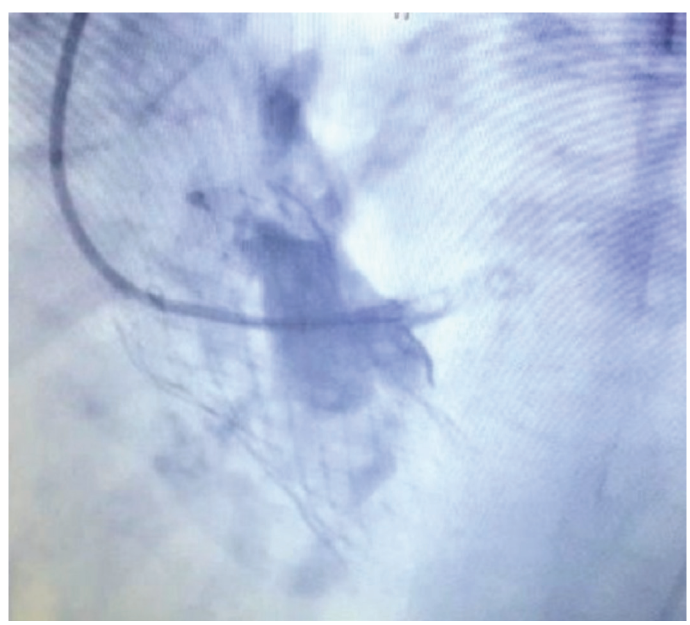

**Figure 4.** Angiographic view of the thrombus in the left coronary ostium

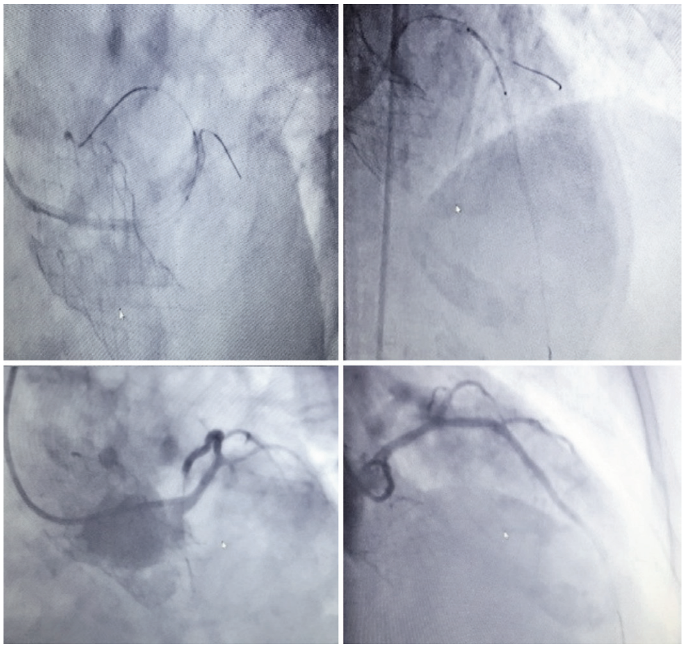

**Figure 5.** In angiographic views, ensuring of the TIMI 2 grade flow in coronary vessels by percutaneous coronary intervention
*TIMI: The Thrombolysis in Myocardial Infarction score*

TAVR procedure and malposition of the device or natural valve leaflets protrusion or plaque migration in natural valve during the procedure may obliterate the coronary ostia(8) due to anatomic factors such as shallow sinuses of valsalva (<30 mm), low localization of coronary ostium (<12 mm), narrow aortic root, presence of plaque in LMCA and serious calcification of aortic valve cusps. In addition advanced age, female sex, co- existing coronary artery disease, balloon-expandable valves and valve-in-valve implantation increase the risk of CO(6,7,9).

DCO is the late occlusion of the coronary ostia after the successful TAVR procedure. DCO is usually detected during angiography, surgery or autopsy. DCO is always associated with the TAVR procedure and its incidence has been reported as 0.22% in the studies of case series(3). Little is known about how pathophysiologic alterations at the macro and microvascular levels lead to long-term DCO. Although the mechanisms of DCO formation are not clear, theoretically these mechanisms are the presence of the device material, late endothelization hypersensitivity reactions, high wall shear stress, blood flow variability and hemodynamic interactions between these factors(8).

In our view, the left main coronary ostium was occluded by thrombus as a complication of TAVR procedure rather than coronary artery diseases. We may explain the thrombus formation in two ways: a) Early opening and closing of prosthetic valves may lead to leaflet thrombosis by blood stasis in the sinus valsalva area and the separated thrombus from the valve leaflet may occlude the coronary ostium due to dynamical blood flow (embolization), b) thrombus formation may occur in the coronary vessels due to intracoronary stasis due to early termination of the diastolic phase causing by the rigid bioprosthesis valve (*de novo* thrombosis)(8). In this report, the presence of AF, senility, normal LMCA in coronary CT imagings and absence of the cardiovascular risk factors may strengthen our view. However, we could not explain which way was responsible for the mechanism of the thrombus formation (by *de novo* thrombosis or embolization) using multidetector CT scanning because of death in the first hour of PCI.

Another important factor associated with CO may be the lack of effective antithrombotic treatment strategies after TAVR procedure. Especially in AF patients with TAVR, who have high risk of thromboembolism, the antiplatelet therapy is more complex. Proposed treatment schemes are based on small studies and expert opinions. In the guidelines, there are inconsistencies and contradictions about which antiplatelet and anticoagulant agents should be used and how long the dual antithrombotic treatment will be continued in patients with AF after the TAVR procedure(10). Therefore, empirical therapy or early termination of dual antithrombotic therapy may also accelerate the thrombus formation in the coronary ostium in this case report.

In conclusion, late thrombus-induced CO after TAVR procedure is very rare and it may lead to serious outcomes. This complication should be considered when a patient undergoes the TAVR procedure and presents with cardiac collapse, myocardial infarction or ventricular arrhythmia.

Inconsistencies and contradictions in treatment strategies may lead to thromboembolic complications after the TAVR procedure, especially in patients with AF. Due to deficiencies in antithrombotic treatment strategies, the patients with high risk may be periodically screened with the multi-detector CT scanning if TTE is not sufficient. In addition, large randomized controlled trials are needed to determine the effective antithrombotic treatment strategies accepted by the large population.

### Ethics

**Informed Consent:** Informed consent was obtained from the patient's family.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: Ö.E., S.Ç.Ş., M.Ş., Concept: S.Ç.Ş., Design: S.Ç.Ş., Data Collection or Processing: Ö.E., M.Ş., Analysis or Interpretation: Ö.E., M.Ş., Literature Search: S.Ç.Ş., Writing: S.Ç.Ş.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# Successful Endovascular Retrieval of a Stent Fragment from the Femoral Artery

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## Abstract

The use of peripheral angiography is very common in the diagnosis and treatment of peripheral artery disease. In this case, we retrieved the fragment of a stent that had fractured during the procedure for peripheral artery treatment. To our knowledge, there is no similar case in the literature. A 58-year-old male patient with diabetes mellitus (10 years) and peripheral artery disease (3 years), who also had a history of coronary artery bypass grafting surgery, applied to our hospital with a complaint of claudication. The ruptured stent fragment in the superficial femoral artery was retrieved using a snare catheter during peripheral angiography (with appropriate modifications). Successful retrieval, no early or late complications, and no problems in follow-up.

**Keywords:** Endovascular treatment, superficial femoral artery, fragmented stent

## Introduction

Endovascular treatment techniques that have been established to have significant success in femoropopliteal segment diseases are being adopted by new centers worldwide; however, risks such as vascular patency lesions persist after the procedure[1]. New approaches are being developed to address these problems, including a promising "nothing left behind" strategy with the help of advanced technologies[2-3].

Although a number of different management options have been described in the literature, today, endovascular treatment (with snare catheters) and surgical exclusion bypass are the most popular methods due to their favorable results in various studies[2-4].

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In this case report, successful retrieval of a ruptured stent graft fragment in a patient, who was not eligible for major surgical intervention, is described. Stent graft fracture or rupture are extremely rare occurrences that may have severe consequences. While surgical methods have been used in the past for the management of such complications, nowadays, retrieval of the embolized catheter fragment via endovascular techniques is frequently preferred, as it has been proven to be easier and safer than surgical methods[3,5-10]. In this case report, we present a patient who was initially asymptomatic after an intervention in which the stent graft fractured and a piece migrated to the right external iliac artery. Endovascular retrieval of the stent graft fragment from the right external iliac artery using a snare catheter was successfully performed without development of any complications.

Embolization of all or some of the materials used during percutaneous intravascular interventional procedures is a rare complication with a serious risk of morbidity and mortality. Snare catheter is usually used in cases with stent migration as identified by coronary angiography. To our knowledge, the snare catheter has not been tried in peripheral artery interventions so far. In our case, we used a snare catheter to retrieve the lost fragment; thus, showing that these catheters can be used in peripheral artery interventions.

## Case Report

A 58-year-old male patient having diabetes mellitus for 10 years and peripheral artery disease for 3 years applied to our hospital with a primary complaint of recently developing claudication. The patient's history revealed that he was a recipient of prosthesis for both hips and he had a history of coronary artery bypass grafting surgery. Due to his complaints and confirmatory results showing the presence of stenosis in the right superficial femoral artery, a stent graft was placed on the patient's right leg. Peripheral angiography was recommended to the patient because of severe claudication on the left leg and very weak pulse from the left femoral artery. Pulse was normal in the right femoral artery. During the procedure, it was planned to enter the right common femoral artery and return to the left femoral artery. A 6F sheath was placed, but with considerable difficulty. Control scopy showed that the sheath was observed to pass through the stent graft (Figure 1).

The presence of a foreign body was suspected in subsequent imaging. It was later discovered that this was a fragment of the stent graft (Figure 2).

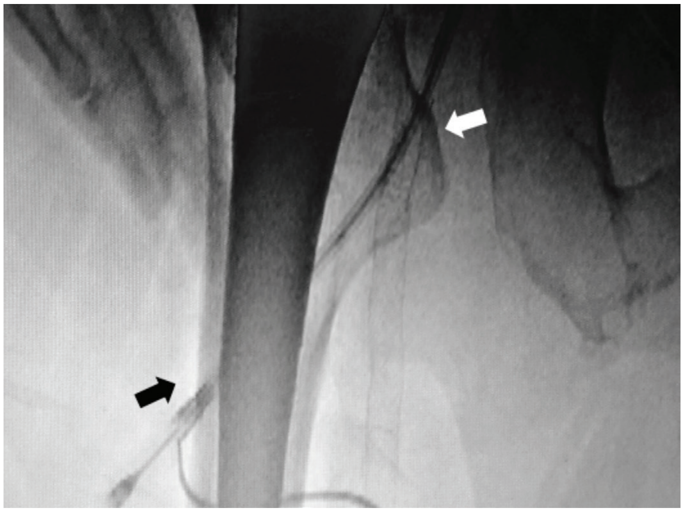

**Figure 1.** Image showing entry through the stent graft in the right femoral artery

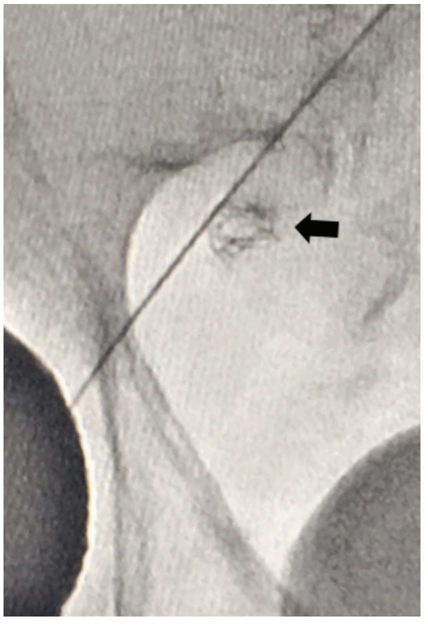

**Figure 2.** Stent fragment is seen in the external iliac artery

The general condition of the patient was good and vital signs were stable. The patient did not have any complaints or pain. We planned to retrieve the stent fragment using a snare catheter with the endovascular technique. A large-diameter snare was chosen in order to ensure that it could hold the ruptured stent fragment; however, a large diameter snare cannot pass through a 6F sheath. Therefore, the 6F sheath in the right femoral artery was replaced with an 8F sheath catheter. We were able to retrieve the stent fragment using a 6 mm snare catheter (Figure 3).

Afterwards, an image was taken with scopy. Flow was normal and no complications developed (Figure 4).

Then we continued with the procedure as usual by inserting a 0.35 hydrophilic guide wire that was turned towards the left femoral artery, and drug coated

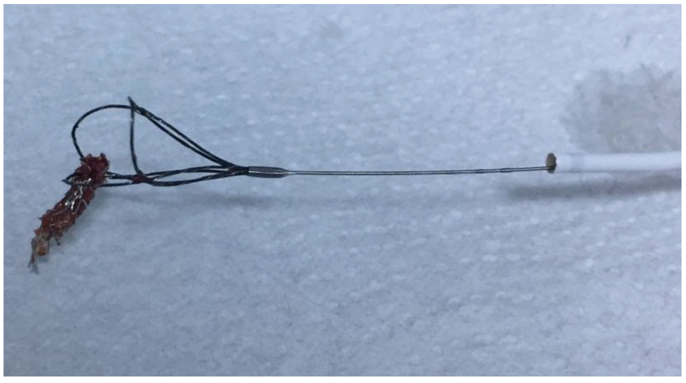

**Figure 3.** Snare catheter and stent fragment are seen

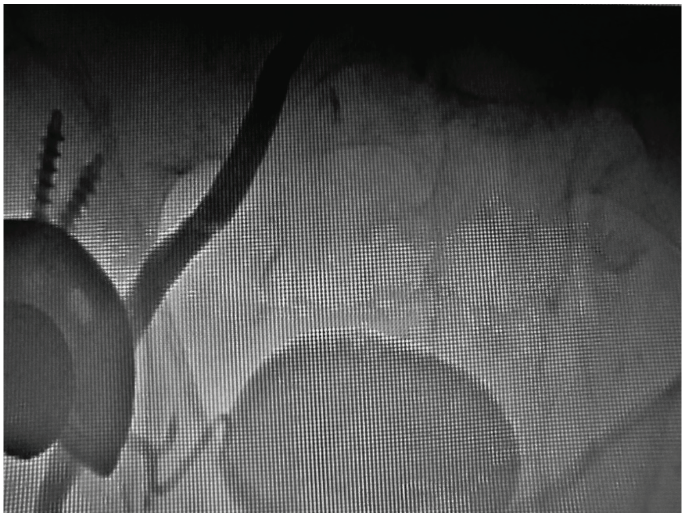

**Figure 4.** Image of external iliac artery after the procedure

balloon was applied to the area with stenosis in the left superficial femoral artery and the stenosis was opened. The procedure was terminated by replacing the 8F sheath in the right femoral artery with a 6F sheath. Finally, the sheath was retrieved 4 hours later. No bleeding or hematoma occurred. The patient was followed with a regular schedule for 3 months.

## Discussion

While open surgery was the only choice in the retrieval of broken and migrated catheters in the past, nowadays, percutaneous transcatheter retrieval of ruptured stent fragments through the use of interventional endovascular techniques have become the primary method of retrieval. They have high success rates and much lower morbidity and mortality rates compared to surgical methods in adult patients. The reported success rate of percutaneous retrieval of intravascular ruptured fragment in the literature is 71-100%[7,11,12]. There are also several alternative tools used for the retrieval intravascular foreign bodies, such as endovascular forceps, retrieval baskets, and pigtail and ablation catheters. However, snare-loop catheter is the most popular option[8-12].

In this case, the right femoral artery was used for entrance to access the lesion in the left femoral artery. This approach was chosen because we knew there was a stent in the right femoral artery. We entered from the upper region, namely, the common femoral artery. However, we recommend performing the procedure under ultrasonography guidance as well as scopy in such cases where stents are present. In fact, it may also be feasible to use the deep femoral artery as a route of entrance; after all, the catheter would be forwarded towards the iliac artery followed by routine approaches. However, since the patient had significant comorbidities, entry from the brachial artery was not considered. Entry from the left lower limb was also out of the question, as the patient had lesions in both the common femoral artery and the popliteal artery on this side. Since the intervention is through the sheath, the sheath can be replaced with a smaller size (e.g., 6F) to avoid complications when the sheath is retrieved at the end of the procedure.

### Ethics

**Informed Consent:** The patient signed the consent form.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: B.D., E.K., Design: B.D., E.K., Data Collection or Processing: B.D., E.K., Analysis or Interpretation: B.D., E.K., Literature Search: B.D., E.K., Writing: B.D., E.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# Rastelli Operation with a Custom-made "Valved Conduit" in an ACHD Case

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In this video, we are presenting a 36 years old woman applied with extreme cyanosis and short of breath followed with mis-diagnosis of a large interventricular septal defect (VSD) and pulmonary hypertension over the years. Having heard a loud and high-pitched pulmonary stenosis murmur on auscultation as a warning sign, the patient was referred to a pediatric cardiologist instead of her routine adult cardiologist. This time the echocardiography revealed a double outlet right ventricle (DORV) with extremely tight pulmonary stenosis and a large canal VSD which is commonly seen in such cases. We decided to close the large VSD with intracardiac tunnel patch and to supply pulmonary flow with a valved conduit as a Rastelli procedure[1-5]. Due to the unavailability of a suitable sized valved conduit during the pandemic, we decided to tailor a custom-made valved conduit mounting size 25 SORIN biologic valve in a 28 mm JOTEC Coated Dacron graft.

The patient could take off cardiopulmonary bypass with positive inotropes and was discharged at two weeks postoperative. She is in New York Heart Association Functional Classification (NYHA) Class I status at fourth postoperative month after discharge.

Double outlet right ventricle is known as a connatural congenital heart disease in which both aorta and pulmonary trunk originate predominantly or entirely from the right ventricle with pulmonary outflow tract obstruction[6].

According to Anderson Classification both preoperative and preoperative assessments revealed as a Taussig Bing type of DORV associated with sub pulmonary VSD with transposition of great arteries[6-8].

After carefully echocardiographic and angiographic assessment of anatomy we decided biventricular repair with Rastelli procedure since both ventricles seemed as adequate size to reconstruct left ventricle outflow tract and right ventricle outflow tract properly[1,2,7,8].

**Keywords:** Rastelli operation, Adult Taussig-Bing, DORV, Custom-made valved conduit

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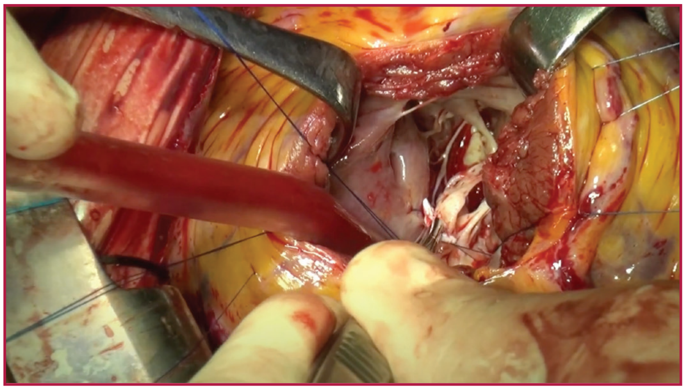

**Video link:**

https://www.youtube.com/watch?v=_vwqX6queEk&has_verified=1

### Ethics

**Informed Consent:** Informed consent was obtained from the patient.

**Peer-review:** Externally peer-reviewed.

**Financial Disclosure:** The author declared that this study received no financial support.

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