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Review Article

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# Role of Septal Myectomy in Pediatric Hypertrophic Cardiomyopathy

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## Abstract

Hypertrophic cardiomyopathy is a prevalent cause of sudden cardiac death among young people. This distinctive genetic condition can manifest at any age from infancy to adulthood. The primary features include unexplained left ventricular hypertrophy coupled with dynamic left ventricular outflow tract (LVOT) obstruction and a variable degree of mitral valve regurgitation. In certain cases, patients may also experience biventricular outflow tract obstruction. Surgical septal myectomy is the gold standard treatment for symptomatic children experiencing severe LVOT obstruction. This review focuses on surgical techniques for septal myectomy in pediatric patients and other adjunct procedures and summarizes the current outcomes.

**Keywords:** Hypertrophic cardiomyopathy, sudden cardiac death, left ventricular outflow tract obstruction, asymmetrical septal hypertrophy, left ventricular myectomy

## Introduction

Hypertrophic cardiomyopathy (HCM), formerly referred to as idiopathic hypertrophic subaortic stenosis, is a primary myocardial disorder with significant genetic component. This condition is marked by dynamic left ventricular outflow tract (LVOT) obstruction and asymmetrical hypertrophy of the interventricular septum (IVS). Although it is relatively rare in children compared with adults, HCM remains one of the leading causes of sudden cardiac death in younger populations. The clinical presentation varies widely from completely asymptomatic to exertional fatigue, chest pain, and/or dyspnea.

Medical management serves as the first-line approach for symptomatic individuals with LVOT obstruction[1];

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however, surgical septal myectomy should be considered for those who do not tolerate or respond adequately to medical therapies[2].

### Morphological Variants

Various forms of septal hypertrophy exist within HCM, including basal (Figure 1), midventricular (Figure 2), and/or apical variants (Figure 3). Diffuse hypertrophy may also occur[3]. Recognizing these patterns is crucial because they influence surgical decisions and approaches. For instance, the basal variant typically involves some degree of mitral valve regurgitation due to systolic anterior motion (SAM) affecting the anterior mitral valve leaflet (AML) (Figure 1). In apical cases, the left ventricular cavity tends to be considerably reduced without SAM.

### Current Indications for Septal Myectomy

Surgical septal reduction continues to be the gold standard in children and young adults with severe LVOT obstruction (LVOT gradient ≥50 mmHg), intolerant to medical therapy, or who fail to respond to medications. In children, currently, there is no role for alcohol septal ablation or novel medical therapy that has been adopted recently in adults[4].

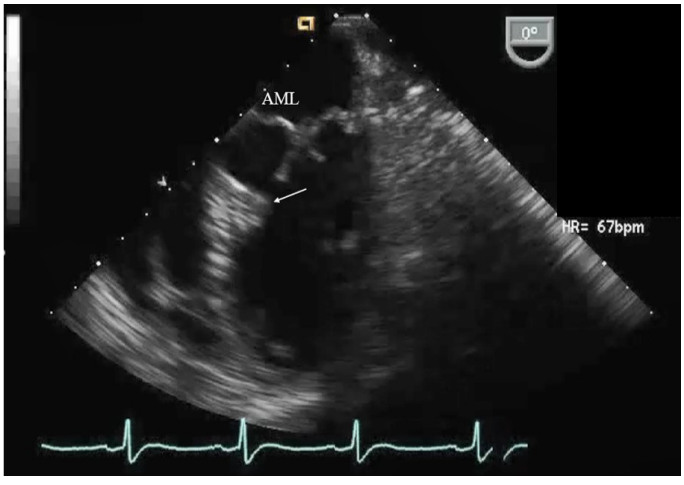


**Figure 1.** Transesophageal echocardiogram showing the characteristic features of hypertrophic cardiomyopathy with systolic anterior motion of the anterior mitral valve leaflet and basal septal hypertrophy (white arrow)
*AML: Anterior mitral valve leaflet*

Surgery should also be considered in the presence of other pathophysiological problems, such as intrinsic mitral valve (MV) disease, fixed subaortic obstruction, and midventricular and/or apical involvement.

### Surgical Technique

As previously noted, the specific pattern of septal hypertrophy dictates the surgical approach necessary to effectively eliminate LVOT obstruction. The procedure typically commences via standard median sternotomy with central cannulation of both the aorta and right atrium. Bicaval cannulation may be used in younger children to enhance their exposure.

Prior to initiating cardiopulmonary bypass (CPB), we routinely assess the LVOT gradient through direct needle measurements taken from both the distal ascending aorta (Figure 4A) and the left ventricle via puncturing through the right ventricular free wall into the IVS (Figure 4B). Gradient assessment occurs at rest and with provocative maneuvers- most frequently through the induction of premature ventricular contractions (PVCs) using the Brockenbrough-Braunwald-Morrow maneuver-which serves to identify dynamic LVOT obstructions.

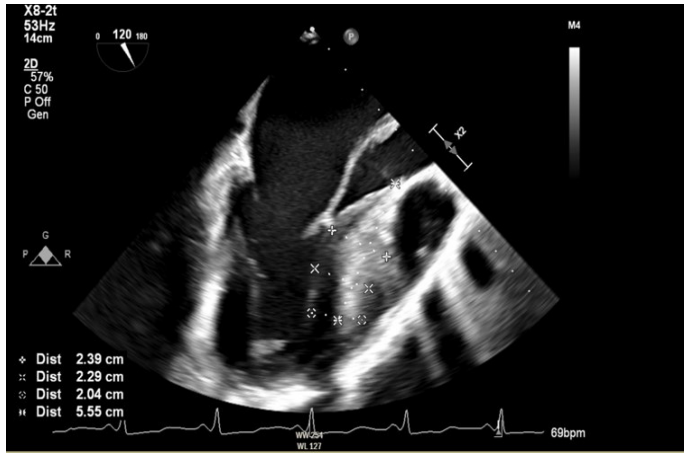


**Figure 2.** Preoperative transesophageal echocardiogram showing the characteristic pattern of hypertrophic cardiomyopathy in a patient with both basal and midventricular hypertrophy. Notice the significant septal thickness and how far it extends into the left ventricular cavity and below the aortic valve. The patient underwent both transaortic and transapical approaches

If PVC induction fails to reveal gradients satisfactorily, medications like isoproterenol may be used. Following CPB cessation, gradient measurements are repeated to ensure effective and complete myectomy and confirm the elimination of significant LVOT gradients (Figure 5B).

## Surgical Approaches

### *Trans-aortic Approach*

This method is particularly effective for basal variants of HCM[5,6]. After achieving cardioplegic arrest, a hockey-stick incision lower than the typical aortotomy utilized for standard aortic valve replacement-extending toward the non-coronary sinus is performed (Figure 6). The first critical step is to thoroughly evaluate the LVOT and to identify any abnormalities within the mitral subvalvular apparatus, such as anomalous chordae or papillary muscles. This is essential because it can cause persistent or recurrent LVOT obstruction.

The initial incision starts just beneath the nadir of the right coronary cusp while considering some distance from its base-this precaution helps prevent future cusp prolapse with subsequent aortic regurgitation (Figure 7). The incision is then directed anticlockwise toward the commissure between the right and left coronary cusps. After initial resection widens the subaortic space, better access to the left ventricle cavity and deeper visualization of the interventricular septum are achieved. The area of resection is then widened until a satisfactory enlargement of the left ventricular cavity is achieved.

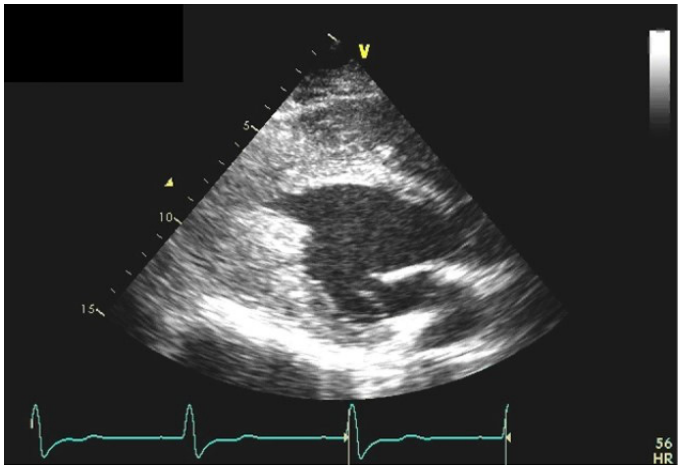


**Figure 3.** Near complete obliteration of the left ventricle apex is a feature of the apical variant of hypertrophic cardiomyopathy

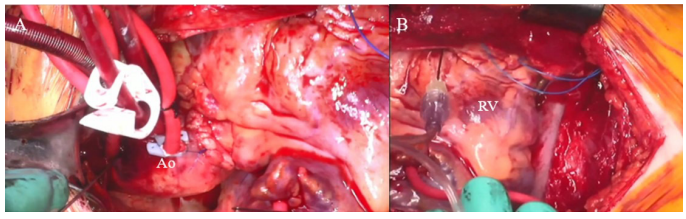


**Figure 4.** Intraoperative images showing the direct assessment of the left ventricular outflow tract gradient before cardiopulmonary bypass. In image **(A)**, a needle is inserted into the distal ascending aorta, while in image **(B)**, a second needle is positioned within the left ventricular cavity, which is accessed indirectly through the right ventricle's free wall and the interventricular septum
*Ao: Ascending aorta; RV: Right ventricle*

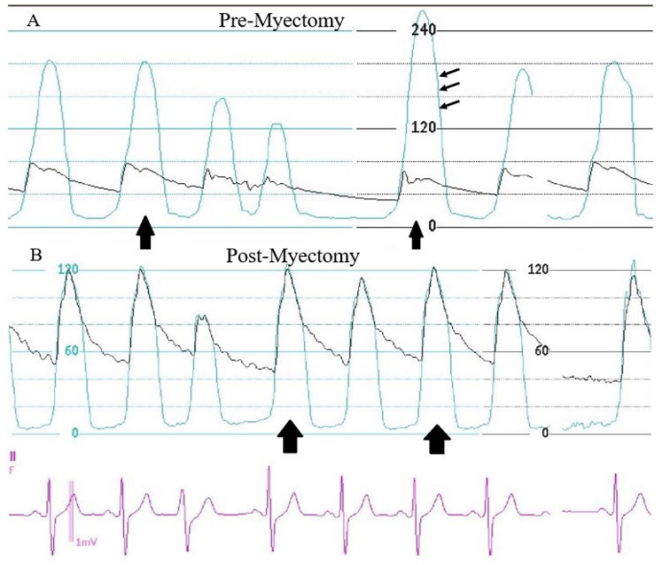


**Figure 5.** Intraoperative pressure tracing reveals: (A) before cardiopulmonary bypass initiation depicting the resting left ventricular outflow tract gradient as measured by direct needle pressures. The light blue line represents left ventricular pressure, whereas the black line indicates aortic pressure. The positive Brockenbrough-Braunwald-Morrow maneuver is indicated (via multiple thin black arrows) through induced premature ventricular contractions, resulting in a notable increase in left ventricular pressure and a decrease in aortic pressure, thereby producing a significant left ventricular outflow tract gradient. (B) presents the tracing following complete septal myectomy, where there is no substantial gradient between the left ventricle and the aorta, indicating a negative Brockenbrough maneuver

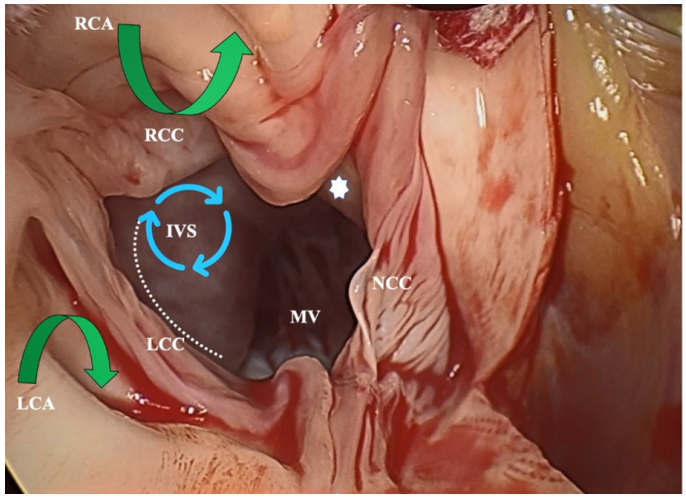


**Figure 6.** The anatomical references for the left ventricular outflow tract were identified following aortotomy and before septal myectomy. The interventricular septum can be observed along with the membranous septum (indicated by an asterisk), which should be preserved during resection. Additionally, the mitral valve is located deep within the left ventricle

*RCA: Right coronary artery ostium, RCC: Right coronary cusp, LCA: Left coronary artery ostium, LCC: Left coronary cusp, NCC: Non-coronary cusp; MV: Mitral valve, IVS: Interventricular septum*

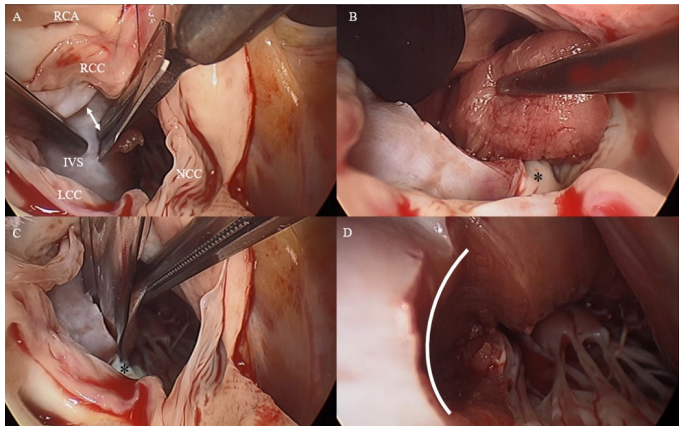


**Figure 7.** The steps of the extended left ventricular septal myectomy via the trans-aortic approach are shown through these operative images. **(A)** the initial incision starts below the nadir of the right coronary cusp and a few millimeters away from the base of the cusp (double head arrow), then it goes toward the left/right coronary commissure, **(B)** the initial resected part of the septum is grasped by the forceps. Notice the very close relationship of the anterior mitral valve leaflet (asterisk), **(C)** The resection is completed by the scissors and **(D)** the area of the initial resection is visualized (trough, white curved line) and notice the marked difference in the thickness of the septum in this area compared with the non-resected portion

*RCA: Right coronary artery ostium, RCC: Right coronary cusp, LCC: Left coronary cusp, NCC: Non-coronary cusp, IVS: interventricular septum*

Additional maneuvers that may enhance exposure include placing a sponge stick against the right ventricular free wall to enhance the visibility of the interventricular septum. This "extended myectomy" when compared with the initial "Morrow" technique, is characterized by its three-dimensional extension that ensures complete elimination of the gradient[7]. Once satisfactory resection is achieved, the aortotomy is closed using a two-layer running suture, followed by a standard de-airing process and removal of the aortic cross-clamp.

## Word of Caution for Children Undergoing Septal Myectomy

It can be challenging in children to perform transaortic myectomy due to the need to navigate through a small aortic root. The surgeon must exercise extreme caution when stretching the root/aortic valve during resection to avoid injuring the cusps or future aortic regurgitation.

Protecting the aortic valve during resection is paramount, and these are a few tips that can help facilitate the procedure:

Placement of the left ventricular vent through the left atrium ensures a dry field and better visualization and minimizes the need for suction through the aortic valve.

Placing a 5/0 or 6/0 polypropylene suture at the base of the cusp into the aortic sinus helps to retract the cusp away from the surgeon's view without the need to add additional instruments through the small aortic root (Figure 8A).

The use of an aortic valve leaflet retractor can protect the cusp until the initial resection is completed, and the surgeon has adequate visualization of the left ventricular cavity (Figure 8B).

After the initial resection, a small retractor can be placed through the created "trough" below the aortic valve to protect the cusp and facilitate retraction (Figure 8C).

### *Trans-Apical Myectomy*

The transapical approach is particularly useful for the midventricular and apical variants of HCM. In these cases, achieving complete resection through the trans-aortic

approach is challenging, if not impossible, especially in patients with small aortic annulus. The technical aspects of this approach have been described in detail elsewhere[8].

Briefly, after cardioplegic arrest, the incision for this approach is placed 1 cm lateral to the left anterior descending coronary artery (Figure 9A) and is more positioned on the left ventricular free wall anteriorly rather than on the actual apex (Figure 9B).

In the true apical variant of HCM, the left ventricular apex is completely obliterated with hypertrophied muscles, and in these cases, initial resection should be limited to the area of the IVS (Figure 9C) to avoid injury to the subvalvular apparatus of the MV, which is usually displaced apically in HCM cases.

After the identification of the left ventricular cavity, additional resection is performed to further enlarge the cavity. The apex is then closed in two layers supported by two strips of Teflon felt (Figure 9D).

### *Trans-Mitral Myectomy*

This approach requires detachment of the anterior leaflet of the MV to expose the IVS, and once resection is completed, patch augmentation of the AML is usually required[9]. One has to be familiar with the anatomy and

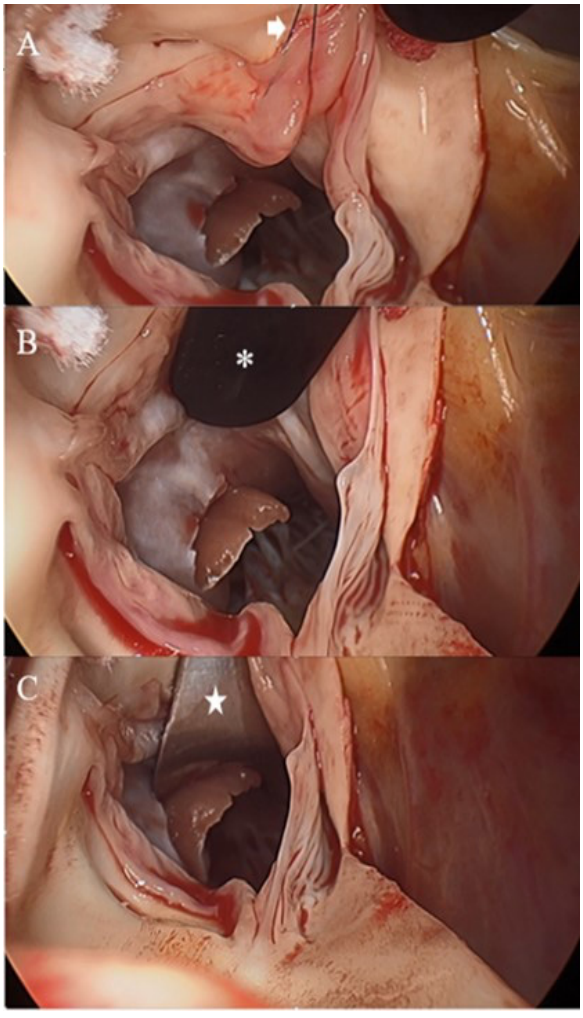


**Figure 8.** Intraoperative photos showing the few tips to protect the aortic valve during myectomy: **(A)** 5/0 or 6/0 polypropylene stitch (white arrow head) can be placed at the very base of the cusp and into the corresponding sinus, which when retracted can elevate the cusp and improve visualization, **(B)** a malleable retractor (asterisk) can be used to protect the right coronary cusp, but it is important to avoid over stretching and forceful retraction of the underlying cusp; and **(C)** once the initial trough is created, placing a low profile retractor with a small lip (white star) under the valve can help expose and protect the cusp at the same time

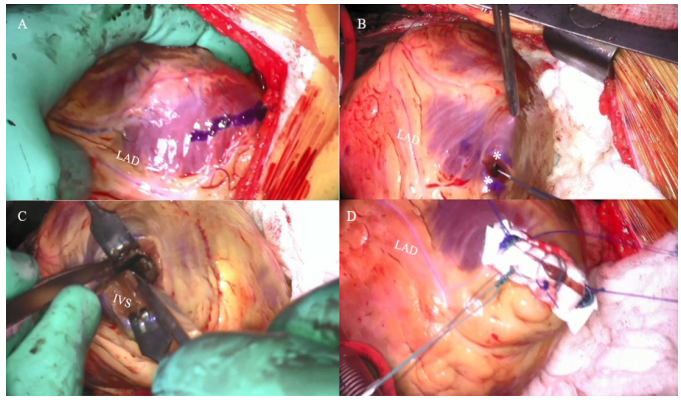


**Figure 9.** Intraoperative images showing the technique of transapical myectomy: **(A)** the apical incision is performed 1 cm lateral to the left anterior descending coronary artery, **(B)** notice the thin edges of the opened apex (asterisk) in this patient reflect the presence of a small aneurysm at the apex, **(C)** the perspective through the exposed left ventricular apex reveals the resected muscle specimen and interventricular septum. It is crucial for the surgeon to remain on the interventricular septum side throughout the resection process until they can clearly identify the papillary muscles associated with the mitral valve, thereby preventing any accidental damage to the subvalvular structures of the mitral valve and **(D)** Final closure of the apical incision, which is performed using a two-layer closure supported by Teflon felt strips

*LAD: Left anterior descending coronary artery, IVS: Interventricular septum*

visualization of the IVS through the MV, as it differs from the commonly used trans-aortic approach. This approach may be particularly useful in children and patients with a small aortic root in which resection and exposure via the transaortic approach are limited. A third potential benefit of this approach is that it allows the treatment of MV pathology and septal myectomy via one incision.

## Adjunct Procedures for Left Ventricular Myectomy

### *Resection of Anomalous Papillary Muscles/Cordae*

As described above, failure to recognize and address these MV abnormalities may result in persistent or recurrent LVOT obstruction[10,11]. In addition, these abnormalities can be difficult to detect on preoperative echocardiography; thus, the initial assessment of the LVOT is key. It is important to distinguish the anomalous from the true papillary muscle of the MV, with the major difference being that the former attaches to the body of the leaflet with no chordal attachment and can therefore be safely excised. Anomalous chordae are easily distinguished from the primary chordal structure of the MV because they insert into the septum and are not attached to the free leading edge of the leaflet. These limitations limit the AML mobility, leading to SAM. It is important to remember that no chordal attachment should occur between the MV apparatus and the IVS.

### *Unroofing of Associated Myocardial Bridging*

Identification of myocardial bridging (MB) in patients with HCM can be challenging, and identifying those requiring unroofing can be even more challenging. There are no clear guidelines or recommendations regarding the best management approach for these patients.

Following septal myectomy, the mid-term results of different treatment modalities for MB in patients with HCM were reported by Wang et al.[12]. There were 823 patients included, with 31 events identified (mortality in 24 and non-fatal myocardial infarction in 7) by the authors. The authors concluded that surgery for MB is advantageous when performed at the time of septal myectomy. Most patients, especially those presenting with chest pain in the setting of HCM, undergo coronary angiography. If a MB is identified, haemodynamic assessment of the bridge is done to determine if it is clinically significant, which will assist in decision-making for a concurrent unroofing procedure. Our technique of MB unroofing is performed via CPB and on the arrested heart in order not to inadvertently damage the coronary artery[13]. Using sharp and electrocautery dissection, we unroof the entire bridged segment (Figure 10). It is important to note that the bridged segment of the coronary artery is fragile, and unroofing should be meticulously performed.

### *Left Ventricular Apical Aneurysm*

Apical and pseudoaneurysms may occur in HCM. They are usually thin walls with varying sizes and can appear dyskinetic or akinetic. It occurs particularly in those with apical and midventricular variants (15-30% of patients)[14]. Identification of these aneurysms is not always straightforward. In an analysis of 1332 patients with apical HCM, the diagnosis of concomitant apical aneurysms on echocardiography was missed in 64.5%[15].

Surgical resection of these aneurysms is recommended at the time of septal myectomy to minimize the risks of ventricular arrhythmias, heart failure, and/or sudden cardiac death, which have been reported in these cases[16].

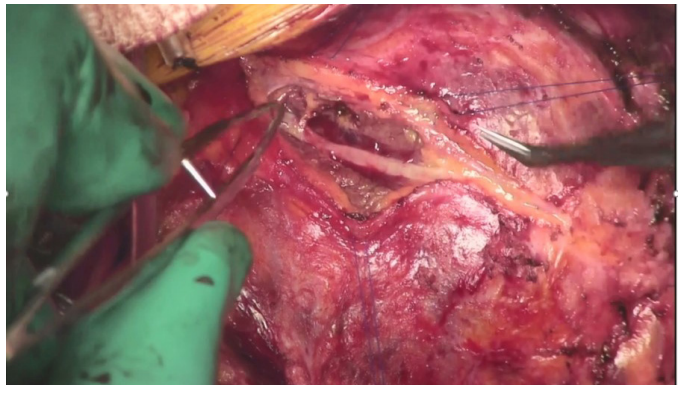

**Figure 10**. Intraoperative photograph of repeat sternotomy with unroofing of a long segment of the left anterior descending coronary artery in a patient with hypertrophic cardiomyopathy who underwent previous septal myectomy. The diagnosis of myocardial bridge in this patient was missed during his first surgery

### *Placement of Epicardial Internal Cardioverter Defibrillators*

In the pediatric population, and due to the limitation of transvenous implantation of internal cardioverter defibrillators (ICD), it is not unusual to place an epicardial system at the end of the septal myectomy procedure (Figure 11). The indications include those with risk factors for sudden cardiac death, history of sustained ventricular tachycardia/fibrillation, and/or septal thickness ≥3 cm[17]. Another option in children is placement of a subcutaneous system[18].

### *Right Ventricular Myectomy*

A specific subset of patients with HCM, particularly those linked to genetic conditions such as Noonan syndrome, may exhibit biventricular outflow tract obstruction. Recognizing this condition is crucial during assessment, particularly when considering left-sided surgical myectomy.

The procedure for septal myectomy on the right side differs from that on the left; notably, due to the presence of septal attachment of the tricuspid valve on the right side. Therefore, caution must be exercised when shaving the IVS on the right side to prevent damage to both the conduction tissue and the tricuspid valve apparatus. Typically, this approach is achieved via an infundibular incision, followed by patch augmentation of the right ventricle outflow (Figure 12) tract[19].

### Outcomes of Septal Myectomy in A Children

Children diagnosed with HCM often exhibit symptoms that resemble those seen in adults. These symptoms predominantly originate from a combination of diastolic dysfunction and notable mitral regurgitation. The initial signs of sudden death occur more frequently in children than in adults[20].

The surgical procedure is technically more complex for pediatric patients because of various anatomical challenges, particularly those related to the small size of the aortic annulus and the LVOT. A study conducted at the Mayo Clinic examined 127 patients aged 2-21 years who underwent septal myectomy. The findings indicated no early mortality; the most prevalent additional procedures included resection of accessory papillary

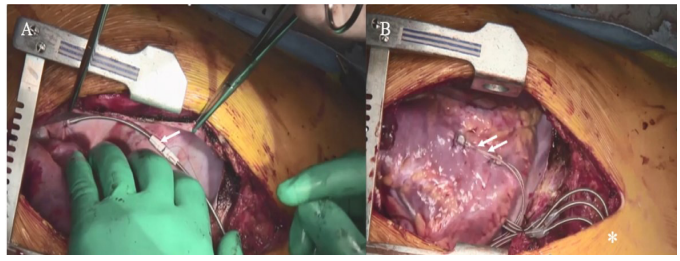


**Figure 11**. For pediatric patients requiring an internal cardioverter defibrillator, the defibrillator implantation is typically performed postmyectomy. During this process, an epicardial system is installed, with the defibrillator coil (indicated by the white arrow in Figure **A)** affixed to the pericardium beneath the phrenic nerve. Concurrently, multiple sensing epicardial leads (depicted by white arrows in Figure **B)** are attached to the epicardial surface of the right ventricle, while the device itself is positioned in the epigastric region behind the rectus abdominis muscle (noted by asterisk)

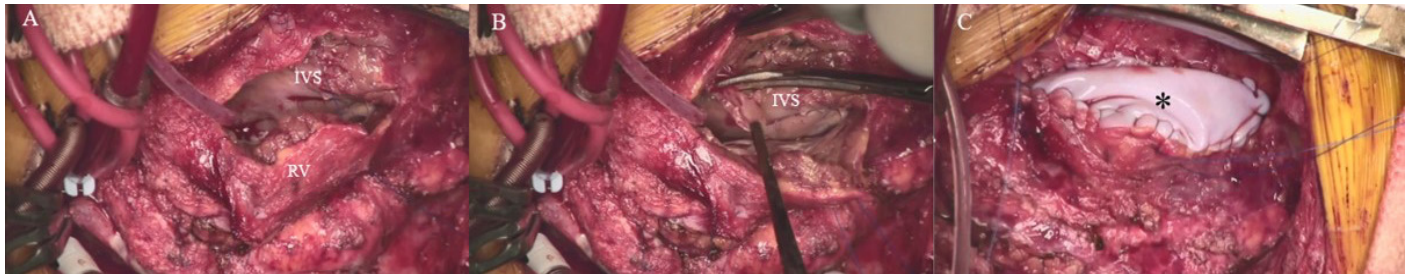


**Figure 12**. Intraoperative photographs showing the technique of right ventricular myectomy, which is performed through an incision in the right ventricular outflow tract **(A)** Limited resection is performed on the right side of the septum **(B)**, followed by patch augmentation (asterisk) of the outflow tract **(C)**

*IVS: interventricular septum; RV: right ventricle*

muscles, repair of the MV, and closure of atrial-level shunts. Complications noted involved two cases of iatrogenic injury to the MV and seven cases involving injury to the aortic valve, all of which were successfully repaired. Additionally, they reported one case of an iatrogenic ventricular septal defect. Although there were four late fatalities, most patients experienced symptom improvement, with 96% classified within New York Heart Association class I or II. Six patients required repeat septal myectomy[21].

### Recurrent Obstruction Following Septal Myectomy

In cases where complete and adequate septal myectomy is performed, recurrence rates tend to be low. As previously mentioned, it is essential to exclude anatomic factors contributing to recurrence-such as mitral subvalvular abnormalities involving anomalous papillary muscles and chordae-during the initial myectomy procedure to prevent reoperation or persistent symptoms.

Specific mechanisms leading to redo myectomy were identified in >50 patients: insufficient initial myectomy (especially critical in younger children), midventricular obstruction, and anomalous papillary muscles[22]. The option for repeat septal myectomy remains both safe and viable; and it should continue to be considered the primary treatment modality for patients experiencing recurrent or persistent LVOT gradients following initial limited resection.

## Conclusion

Extended left ventricular septal myectomy remains the gold standard for treating symptomatic children diagnosed with the obstructive variant of HCM. The trans-aortic and/or transapical approaches are most commonly used in this population, depending on the IVS morphology and the level of obstruction. Other adjunctive procedures that may be considered include concomitant unroofing of significant MB and placement of epicardial ICD in patients who meet the criteria. Concomitant right ventricular outflow tract obstruction, especially in patients with genetic syndromes. The outcomes remain excellent with low risk of recurrence if complete and satisfactory myectomy is initially performed.

### Ethics

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# Assessment of the SYNTAX Score II in Patients with Non-ST Elevation Myocardial Infarction Who Have Coronavirus Disease-2019

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## Abstract

**Objectives:** The objective of this research was to investigate the correlation between the SYNTAX score II (SS-II), a measure of the occurrence of coronary artery disease and mortality over a 4-year period, and factors that increase the susceptibility of individuals to atherosclerosis in coronavirus disease-2019 (COVID-19) patients diagnosed with non-ST-elevation myocardial infarction (NSTEMI).

**Materials and Methods:** We retrospectively examined 200 NSTEMI patients with COVID-19 who applied to Adıyaman Training and Research Hospital between 01.07.2021 and 01.11.2021. We recorded demographic data (age, gender), comorbid diseases, laboratory parameters (hemogram, biochemistry, serological test results), thorax computed tomography findings (COVID-19-compatible or not), angiography results, intervention needs, and mortality status. COVID-19 was confirmed by positive reverse transcription polymerase chain reaction. All patients had SS values and SS-II values calculated. Based on a median SS II value of 28.5, the patients were classified into the low and high SS-II groups.

**Results:** The high-SS-II group exhibited elevated total cholesterol, low-density lipoprotein, carotid intima-media thickness (CIMT), and left ventricular ejection fraction values ($p<0.001$). Logistic regression analysis revealed that CIMT (odds ratio: 3.124, 95% confidence interval: 1.744-5.628; $p<0.001$) was an independent predictor of SS-II.

**Conclusion:** In patients with NSTEMI and COVID-19, CIMT and SS-II might increase the risk of atherosclerosis. The combination of NSTEMI and COVID-19 increases mortality.

**Keywords:** Coronavirus disease-2019, non-ST elevation myocardial infarction, SYNTAX score II

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## Introduction

Hubei Province's Wuhan province announced a new coronavirus epidemic in December 2019. This sickness spreads uncontrollably. Coronavirus disease-2019 (COVID-19) most often affects the respiratory system, whereas cardiac dysfunction often draws attention to the cardiovascular (CV) system[1]. In an extensive case series, older patients with CV died the most and were most affected by the pandemic[2]. A thorough COVID-19 case count of 72.314 was obtained from the Chinese Center for Disease Control and Prevention. Of 87% of 30-to 79-year-olds, 2.3% died. Mortality was 8% for patients aged 70-79 years and 14.8% for those aged 80+. Comorbidities increased diabetes CV mortality (10.5%)[1,3].

COVID-19 causes myocardial infarction (MI), myocarditis, heart failure (HF), arrhythmia, and venous thromboembolism. Risk-averse patients with CV infection with COVID-19 postpone hospital admission, which worsens outcomes[4,5]. On myocardial cells, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can cause cardiac dysfunction. On angiotensin-converting enzyme 2 receptors, the virus strongly activates the innate immune system, producing proinflammatory cytokines and inducing systemic inflammation. A "cytokine storm" causes widespread endothelium and procoagulant activity[6]. Local and systemic coagulation, platelet activation, and immunothrombosis increase with SARS-CoV-2 infection[7].

The severity of non-ST-elevated MI (NSTEMI) is dependent on clinical and laboratory findings[8]. Coronary atherosclerosis causes NSTEMI. Clinical decision-making depends on risk categorization. Early risk, clinical syndrome, and therapy for NSTEMI determine mortality[9]. Risk scoring is used by acute coronary syndrome (ACS) cardiologists to assess coronary artery disease (CAD) severity and complexity[9]. The lack of clinical factors in the SYNTAX score (SS) has been recognized as a notable constraint when used for patients with intricate CAD in terms of classification ability. Recently, researchers have created SS-II as a new solution to overcome this constraints[10]. Researchers have linked SS-II to both angiographic (anatomic SS) and clinical factors, including age, gender, left ventricular ejection fraction (LVEF), creatinine clearance, chronic obstructive pulmonary disease (COPD), and peripheral vascular disease[11]. The application of this method allows for a more precise and personalized prediction of mortality, resulting in a clinically valuable tool for making decisions at the patient's bedside and managing complex CAD[12].

To our knowledge, no study has examined the SS-II score for predicting lesion complexity in NSTEMI patients who survived COVID-19 without sequelae. Therefore, we believe our study will add to the literature. Therefore, we thought it appropriate to conduct a study on SS-II analysis in such patients.

## Materials and Methods

### Study Design

We retrospectively examined 200 NSTEMI patients with COVID-19 who applied to Adıyaman Training and Research Hospital between 01.07.2021 and 01.11.2021. The local ethics committees approved this Declaration of Helsinki-compliant study. Ethics committee approval was obtained from the Ethics Committee of Adıyaman University Non-Invasive Clinical Research (approval no.: 2021/04-15, date: 20.04.2021). All patients gave informed consent. We selected 213 patients with NSTEMI who underwent coronary angiography (CA) for the study. After determining the exclusion criteria, we admitted 200 consecutive eligible patients to our coronary care unit. At least 48 hours of cardiac troponin levels exceeding the 99$^{th}$ percentile upper reference limit and new or worsening chest discomfort at rest or with moderate effort defined NSTEMI. Abnormal chest discomfort occurred for more than 20 minutes, new-onset angina occurred, and its frequency, duration, and severity were increased. Heart troponin was detected at 0.04 ng/mL on the Alere Triage MeterPro [(Alere Inc., San Diego, California, United States of America (USA)]. The SS, which uses natural coronary arteries, has been found to exclude the recent coronary

artery bypass graft patients[13]. None had cardiogenic shock. Intrastent restenosis is also classified as de novo lesions. We recorded demographic data (age, gender), comorbid diseases, laboratory parameters (hemogram, biochemistry, serological test results), thorax computed tomography findings (COVID-19-compatible or not), angiography results, intervention needs, and mortality status. COVID-19 was confirmed by positive reverse transcription polymerase chain reaction (RT-PCR).

### Study Protocol

Use of antihypertensive medication or arterial blood pressure >140/90 more than once defines hypertension (HT). Diabetes mellitus (DM) as ≥126 mg/dL fasting blood glucose or current antidiabetic medication use. Hyperlipidemia was diagnosed in patients with total cholesterol >200 mg/dL, triglycerides >150 mg/dL, and dyslipidemia or antilipidemic therapy. Active smoking was defined as 1 pack per year until 1 month before trial participation. Sudden cardiac death in male or female first-degree relatives under 55 or 65 was considered chronic HF. In the apical 4-chamber view, M-mode echocardiography measured the LVEF. Body mass index was calculated as weight in kg divided by height in meters squared.

In numerous angulated views, the Judkins method was used for femoral selective CA at 30 frames/s (Allura Xper FD10; Philips Healthcare, Best, The Netherlands). Separately, two invasive cardiologists evaluated coronary angiograms under clinical blinding. At least 50% luminal diameter stenosis in one major coronary artery is considered a significant vascular disease. For coronary lesions with a diameter stenosis ≥50% in arteries ≥1.5 mm, scores were required. In interventional cardiology, SS was determined using tertiles (<32, >32). We defined SS-II [percutaneous coronary intervention (PCI) and bypass] based on patient clinical characteristics[6]. Based on a median SS-II value of 28.5, the patients were classified into the low and high SS-II groups.

### Statistical Analysis

Statistic calculations were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, New York, USA). Categorical variables were calculated using numbers and ratios. Mean ± standard deviation was used for regularly distributed data, whereas median (interquartile range) was used for non-normally distributed data. The Kolmogorov-Smirnov test confirmed data normality. Student's t-test and Mann-Whitney U test were used to compare the two groups. Categorical variables were tested using the chi-square. The multivariate logistic regression analysis included possible risk factors identified by the univariate logistic regression analysis ($p<0.25$). Finally, forward logistic regression identified the most dissimilar factors between the groups. $P<0.05$ qualifies as statistically significant.

## Results

The study included 200 patients with NSTEMI (mean age: 62.3±12.5 years, 65% male). Table 1 shows baseline demographic and clinical data according to SS-II for the research population. Smoking, HT, DM, COPD, peripheral arterial disease, previous PCI, stroke, and family history were significantly more frequent in the high SS-II group ($p<0.001$). The low SS group had a higher proportion of men, whereas the high SS-II group had a higher average age ($p<0.001$). The high SS-II group exhibited elevated total cholesterol, low-density lipoprotein (LDL), carotid intima-media thickness (CIMT), and LVEF values ($p< 0.001$). The groups exhibited similar values for high-density lipoprotein (HDL) and triglyceride (TG) levels and medication rates ($p>0.05$).

Table 2 lists the parameters of the univariate linear regression analysis and the statistical evaluations. CIMT, HDL, LDL, and HT were independently associated with SS-II. Furthermore, logistic regression analysis revealed that CIMT (odds ratio: 3.124, 95% confidence interval: 1.744-5.628; $p<0.001$) was an independent predictor of SS-II.

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

| | Low SS-II (n=100) | High SS-II (n=100) | p-value |
|---|---|---|---|
| **Age, years** | 59.1±0.8 | 65.1±0.3 | **<0.001** |
| **Gender, male, n, (% )** | 70 (70) | 60 (60) | **<0.001** |
| **Previous PCI history, (%)** | 42 (42) | 49 (49) | **<0.001** |
| **Family history, %** | 10 (10) | 19 (19) | **<0.001** |
| **BMI, kg/m²** | 27.4±0.6 | 28.1±1.1 | 0.356 |
| **DM (%)** | 22 (22) | 28 (28) | **<0.001** |
| **HT (%)** | 46 (46) | 51 (51) | **0.008** |
| **PAD (%)** | 25 (25) | 42 (42) | **<0.001** |
| **COPD (%)** | 43 (43) | 50 (50) | **<0.001** |
| **Smoking (%)** | 40 (40) | 47 (47) | **<0.001** |
| **Glucose (mg/dL)** | 115.5±54.3 | 128.5±58.4 | 0.072 |
| **GFR (mL per min/1.73 m²)** | 61.1±1.5 | 74.1±1.8 | 0.096 |
| **TC, mg/dL** | 162 (42-200) | 186 (57-236) | **<0.001** |
| **HDL, mg/dL** | 42 (12-48) | 38 (10-44) | 0.092 |
| **LDL, mg/dL** | 101 (34-122) | 127 (42-156) | **<0.001** |
| **TG, mg/dL** | 125.35 (69.9-116) | 133.8 (80.25-156) | 0.652 |
| **CIMT** | 0.73±0.26 | 0.97±0.3 | **<0.001** |
| **LVEF (%)** | 51.1 0.7 | 46.3±0.8 | **<0.001** |
| **Medications** | | | |
| ACEI (%) | 25 | 25.8 | 0.522 |
| BB (%) | 6.5 | 7.1 | 0.456 |
| CCB (%) | 8.7 | 9.4 | 0.324 |
| ASA (%) | 17.4 | 16.8 | 0.371 |
| Statin (%) | 16.2 | 17.6 | 0.666 |

*p-value<0.05*
*PCI: Percutaneous coronary intervention, SS-II: SYNTAX score II, BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, PAD: Peripheral arterial disease, COPD: Chronic obstructive pulmonary disease, GFR: Glomerular filtration rate, TC: Total cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglyceride, CIMT: Carotid intima-media thickness, LVEF: Left ventricular ejection fraction, ACEI: Angiotensin-converting enzyme inhibitor, BB: Beta blocker, CCB: Calcium channel blocker, ASA: Acetyl salicylic acid*

**Table 2.** Factors associated with SS-II

| **Linear regression analysis** | | | | **Logistic regression analysis** | | |
|---|---|---|---|---|---|---|
| | **Coefficients** | **95% CI** | **p-value** | **OR** | **95% CI** | **p-value** |
| **CIMT** | 5.202 | 3.16-10.2 | **<0.001** | 3.124 | 1.744-5.628 | <0.001 |
| **HDL** | 0.128 | -0.025-0.622 | **0.042** | | | |
| **LDL** | 0.902 | 0.542-1.256 | **0.029** | | | |
| **HT** | 0.524 | 0.324-2.960 | 0.056 | | | |

*Variables with p<0.25 in univariate regression were included into multivariate regression*
*SS-II: SYNTAX score II, CI: Confidence interval, OR: Odds ratio, CIMT: Carotid intima-media thickness, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HT: Hypertension*

## Discussion

This study examined the correlation between SS-II and CIMT in patients with NSTEMI and COVID-19. The primary conclusions of this investigation were as follows: (i) There was a strong correlation between SS-II and CIMT, and (ii) CIMT is a reliable indicator of SS-II.

The COVID-19 pandemic has severely impacted healthcare services, limiting patient access, halting elective procedures, and causing patients to hesitate to visit hospitals due to infection transmission, particularly in NSTEMI[14,15]. Chronic illnesses COVID-19 increase risk and mortality. Ischemic heart disease, HT, HF, and atrial fibrillation are more common in COVID-19 deaths[16].

COVID-19 patients with elevated cardiac troponin levels, echocardiographic abnormalities, and electrocardiograms have reported acute myocarditis. Cardiac histopathological findings in deceased patients include inflammatory and prothrombotic features, damage from previous conditions, and myocardial hypertrophy. A significant proportion of patients with COVID-19 have increased high-sensitivity cardiac troponin (hs-cTn) levels, with over 50% of those who died having hs-cTnI levels above 28 mg/mL. We recommend searching for other clinical features because troponin elevation alone does not diagnose ACS. CA is recommended for patients with inflammatory marker values. Patients whose CT scan results were not compatible with COVID-19 and whose RT-PCR test was negative also required more intervention. Laboratory tests, RT-PCR test results, and thorax CT findings do not have a statistically significant effect on the requirement for CA[17-19].

A study by Majeed et al.[20] found that patients with NSTEMI and COVID-19 had a higher inpatient mortality rate, longer length of stay, and fewer invasive cardiac procedures. Despite lower underlying cardiac and pulmonary comorbidities, these patients have a five-fold mortality risk. COVID-19 can lead to various clinical symptoms, including MI, myocarditis, HF, arrhythmias, and venous thromboembolism. Cardiac damage in COVID-19 infections is attributed to mechanisms such as inflammation, cytokine storms, increased coagulation functions, and an imbalance between oxygen supply and demand[21].

The SS angiographic scoring instrument ranks coronary lesions by complexity. Patients with stable CAD, multivessel disease, or complicated coronary lesions were tested first. The SS-II grading system, which combines anatomical SS and clinical factors, may better predict clinical events[22]. Song et al.[23] found SS-II better than SS for predicting 2-year death in patients with complicated CAD, and Salvatore et al.[24] showed it may predict unfavorable clinical outcomes in patients with severe CAD. Combined anatomical and clinical characteristics favored anatomical SYNTAX. Through cardiac bypass or PCI risk rating, SS-II was found to predict 4-year mortality. Age, creatinine, and ejection fraction enhanced SYNTAX adverse event prediction. Lower LVEF, creatinine clearance, anatomical SS, younger age, and female sex were favorable markers for coronary bypass in the SYNTAX research[25-27]. CIMT, an atherosclerosis measure, was significantly correlated with SS-II in our research.

Hayiroglu et al.[28] observed that SS-II was associated with in-hospital mortality and major adverse cardiovascular events (MACE). To predict target lesion revascularization, stent thrombosis, or recurrent MI, SS-II is a poor predictor. We did not assess individuals with long-term MACE who tested positive for COVID-19 in cases of NSTEMI.

### Study Limitations

The SS-II score in patients with COVID-19 and NSTEMI has several drawbacks. Hypercoagulability due to COVID-19 increases thrombosis risk. This may make CAD severity assessment and revascularization decisions more difficult, underestimating CAD's complexity. Inflammation due to COVID-19 can worsen CV problems. This heightened inflammatory state can alter the presentation and prognosis of patients with NSTEMI, whereas the SYNTAX II score does not. In patients with severe COVID-19, hemodynamic instability

may occur. This may cause SS-II score errors because it can complicate angiographic interpretation and coronary architecture assessment. COVID-19 can damage, inflame, and cause stress in the heart. The SS-II does not include these conditions, prioritizing anatomy over function. Catheterization laboratories and specialized staff may be scarce during the COVID-19 pandemic. Rapid or accurate patient assessment could potentially impact the SS-II. SS-II predicts long-term results using anatomical and clinical characteristics. COVID-19 increases the risk of serious respiratory problems and longer hospital admissions, which can change the outcome. COVID-19's symptoms and severity of COVID-19 affect NSTEMI's clinical appearance. Due to this unpredictability, a standardized scoring system like SS-II may not adequately represent the clinical context of these patients.

## Conclusion

The correlation between CIMT and SS-II in patients with COVID-19 diagnosed with NSTEMI might provide useful insights into their susceptibility to atherosclerosis. The correlation between NSTEMI and COVID-19 is a significant contributor to the increase in mortality rates.

### Ethics

**Ethics Committee Approval:** Ethics committee approval was obtained from the Ethics Committee of Adıyaman University Non-Invasive Clinical Research (approval no.: 2021/04-15, date: 20.04 2021).

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

### Authorship Contributions

Surgical and Medical Practices: Tanrıverdi O, Concept: Aşkın L, Design: Şengül Aşkın H, Data Collection and/or Processing: Tanrıverdi O, Analysis and/or Interpretation: Aşkın L, Literature Search: Aşkın L, Şengül Aşkın H, Writing: Tanrıverdi O.

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Research Article

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# Influence of Pre-Electrical Cardioversion Potassium Test Timing on Ventricular Arrhythmic Complications and Success Rates

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## Abstract

**Objectives:** Elective electrical cardioversion (ECV) is frequently used for supraventricular tachycardia therapy. However, the success rate of this approach varies, and ventricular arrhythmias may develop as a consequence. We aimed to determine whether the timing of pre-ECV potassium serum testing affects patient outcomes.

**Materials and Methods:** This retrospective cohort study analyzed 65 patients who underwent elective ECV in 2023. Patients were divided into two groups (short-interval vs long-interval) based on the median time (in days) between the potassium test and ECV. The primary outcome measure was the incidence of ventricular arrhythmias, whereas the secondary outcome measure was immediate restoration of sinus rhythm.

**Results:** The median time between the potassium test and ECV was 57 (interquartile range 135) days. No ventricular arrhythmias were observed. There was no statistically significant difference in success rates between the two groups (84.8% versus 84.4%; p=0.958; $\chi^2$ test). Predetermined risk factors for potassium disturbances did not influence success rates.

**Conclusion:** Our study suggests that the timing of potassium serum testing does not influence the occurrence of ventricular arrhythmias following elective ECV. In addition, the timing of serum potassium testing did not influence the success rate. Therefore, potassium testing shortly before cardioversion may not be necessary.

**Keywords:** Electrical cardioversion, potassium, ventricular arrhythmias, serum testing

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## Introduction

Electrical cardioversion (ECV) is a medical procedure that was first performed in the 1950s[1]. To this day, ECV remains a fundamental intervention in the management of various cardiac arrhythmias. The objective of ECV is to administer an external electric shock that depolarizes all excitable cardiac cells, rendering them refractory, interrupting the re-entry circuit responsible for the arrhythmia, and allowing the sinoatrial node to restore sinus rhythm. In the Canisius-Wilhelmina Ziekenhuis (CWZ) alone, approximately 400 elective ECVs are conducted annually. Immediate success rates are typically quite high, varying from 69.4% to 94.2%[1,2]. Although uncommon, ventricular arrhythmias can occur as a direct complication of ECV and pose significant risks to patients.

Potassium is an essential electrolyte that is mostly found intracellularly in cardiac cells and plays a major role in cardiac electrophysiology. It participates in maintaining the resting membrane potential and repolarization of the cell membrane after each action potential. When extracellular potassium concentration is high, the resting membrane potential is depolarized, leading to spontaneous depolarization. When extracellular potassium concentration is low, the cell membrane becomes hyperpolarized and the conduction velocity and rate of diastolic depolarization[3]. In this way, disturbances in extracellular potassium can cause cardiac arrhythmias. Hence, potassium levels are strictly regulated. However, certain conditions and medications can pose a threat to the potassium balance. For example, commonly prescribed antihypertensive drugs like angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) inhibit the renin-angiotensin system, causing a decrease in aldosterone production. This condition causes less efficient urinary potassium excretion and can potentially lead to hyperkalemia. Moreover, patients with impaired renal function may also have problems excreting potassium, potentially causing hyperkalemia. A study found that among participants in the Dutch general population aged between 65 and 74 years, the prevalence of hypokalemia was 2.7%, whereas the prevalence of hyperkalemia was 0.2%[4].

Given the importance of potassium in cardiac electrophysiology, serum potassium levels may also influence the onset of arrhythmias following ECV. Moreover, one study found that intravenous injection of potassium and magnesium before the start of ECV might positively impact the procedure's success rate[5]. However, current guidelines and the CWZ protocol do not provide any recommendations regarding the monitoring or administration of potassium prior to ECV[6]. Nevertheless, most patients in the CWZ undergoing elective ECV have a recorded serum potassium level, although the timing of these measurements can vary, with some having a recent measurement and others having a less recent. This study aimed to gain more insight into how the timing of serum potassium testing affects arrhythmic complications and the success rate of elective ECV.

## Materials and Methods

### Study Design and Participants

Due to the retrospective nature of the study, ethics committee/IRB approval was waived. However, informed consent from the patient was received according to the ethical principles of the Declaration of Helsinki. The study was assessed by the Local Ethics Committee and registered in the context of transparency. A list of 108 patients who underwent ECV between February and August 2023 was acquired. Eligible participants were >18 years of age, had a documented serum potassium level, and had undergone ECV. The exclusion criteria were use of cardiac implantable electronic devices and active ventricular arrhythmias.

The median time (in days) from the potassium test to ECV was determined to divide patients into two groups. The group with a time interval less than the median was referred to as the "short interval group", while the group with a time interval exceeding the median was referred to as the "long interval group".

### Cardioversion Protocol

In accordance with the European Society of Cardiology guidelines, all patients who had been experiencing atrial fibrillation (AF) for longer than 48 hours underwent pretreatment with oral anticoagulation therapy for a minimum of 3 weeks. The attending anesthesiologist sedated patients by intravenous Propofol administration. Paddles were positioned in an anterior-apical position, and ECV was performed using biphasic shock. The specific starting volume of joules delivered was determined by a nurse specialist. If necessary, additional shocks were administered following the step-up protocol, with a maximum of three shocks administered per session. Patients were monitored using telemetry for 1 hour before discharge.

### Data Collection and Variable Selection

A database was constructed using data extracted from the electronic health record (EHR). Various demographic and clinical characteristics were assessed to compare baseline characteristics between the two groups. For comorbidities, a history of heart failure, diabetes, or coronary artery disease was considered. Specifically, diabetes type II was chosen because multiple studies have shown that this disease is an independent factor that negatively influences the immediate success rate of ECV[7,8]. The presence of comorbidities was determined based on the clinical notes in the patient EHR. Coronary artery disease was defined as typical angina pectoris, acute coronary syndrome, significant stenosis on angiogram, and previous coronary revascularization therapy. Heart failure comprised both preserved ejection fraction and reduced ejection fraction. Impaired renal function was documented because it is known to cause hyperkalemia. This impairment was defined as an estimated glomerular filtration rate <60 mL/kg/1.73m² measured with the chronic kidney disease epidemiology collaboration method.

Furthermore, we documented the use of anti-arrhythmic drugs (AADs). Type III AADs improve the success rate of acute restoration of sinus rhythm[9], thereby making them a significant baseline characteristic. We also documented the use of ACE inhibitors, ARBs, and diuretics because these medications are known to cause disturbances in serum potassium levels and thus may influence serum potassium levels during ECV.

### Outcome Measures

The primary outcome measure was the onset of a new arrhythmia as a direct complication of the ECV, which was defined as ventricular tachycardia (VT), ventricular fibrillation (VF), or Torsade de Pointes.

The secondary outcome measure was the ECV success rate. Successful cardioversion was defined as a restored sinus rhythm immediately after cardioversion. Both outcomes were measured by 12-lead ECG immediately after cardioversion and were examined by an attending nurse specialist.

### Statistical Analysis

Categorical variables are expressed as counts and percentages, whereas continuous variables are expressed as means and standard deviations. To examine differences in characteristics between the short and long interval groups, the chi-square test was used for categorical values. However, in cases in which one or more cells had expected counts of less than five, we opted for Fisher's exact test to ensure the reliability of our test. A Shapiro-Wilk test was performed to determine whether continuous variables followed a normal distribution. For normally distributed continuous data, an independent sample t-test was conducted, and for non-normally distributed data a Mann-Whitney U test was performed. P-value 0.05 was considered statistically significant. All analyses were performed using IBM SPSS version 24.

## Results

### Participants

After selecting patients and reviewing the EHRs, a total of 65 patients were included. Figure 1 presents the

details of participant enrollment. The median time from potassium serum test to ECV was 57 (interquartile range 135), which split the patients into two groups: the short-interval group and long-interval group.

Figure 2 presents the spread of the time interval in days between the potassium test and ECV, as depicted in the boxplots. Table 1 lists the baseline characteristics. There were no statistically significant differences in demographic and clinical baseline characteristics observed. The majority of patients were male and were treated with class II AADs. In the long-interval group, one patient experienced mild hyperkalemia and two patients experienced mild hypokalemia. In the short-interval group, no potassium disturbances were observed.

### Ventricular Arrhythmia Complications

In this study, the primary outcome of interest was the occurrence of VTs and conduction disorders directly following ECV. Our analysis revealed that none of the participants experienced VF, VT, or Torsade de Pointes.

### Immediate Success of ECV

In our cohort, restoration of sinus rhythm immediately after ECV was achieved in 55 (84.6%) patients. In the short-interval group, ECV was successful in 28 cases compared with 27 cases in the long-interval group (84.8% versus 84.4%; p=0.958). Patients with decreased renal function did not exhibit significantly different success rates following ECV compared with those with normal renal function (83.3% versus 84.9%; p=0.892). In total, 29 patients (44.6%) were using either ACE inhibitors or ARBs. Among these patients, the success rate was 89.7%, whereas it was 80.6% for those not using these medications; this was not statistically different (p=0.312). When comparing success rates between patients who were using loop or thiazide diuretics and those who were not, no statistically significant difference was observed (81.8% versus 85.2%; p=0.778).

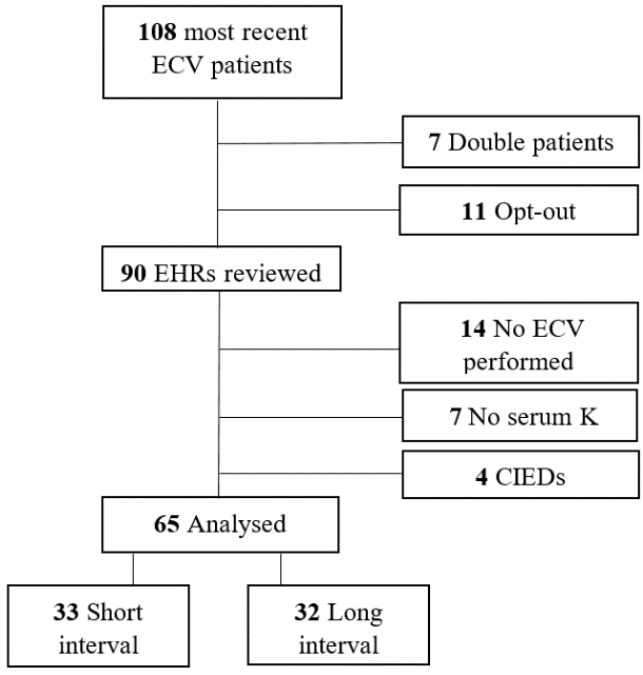


**Figure 1.** Enrolment
*ECV: Electrical cardioversion, EHR: Electronic health record, K: potassium, CIED: Cardiac implantable electronic device*

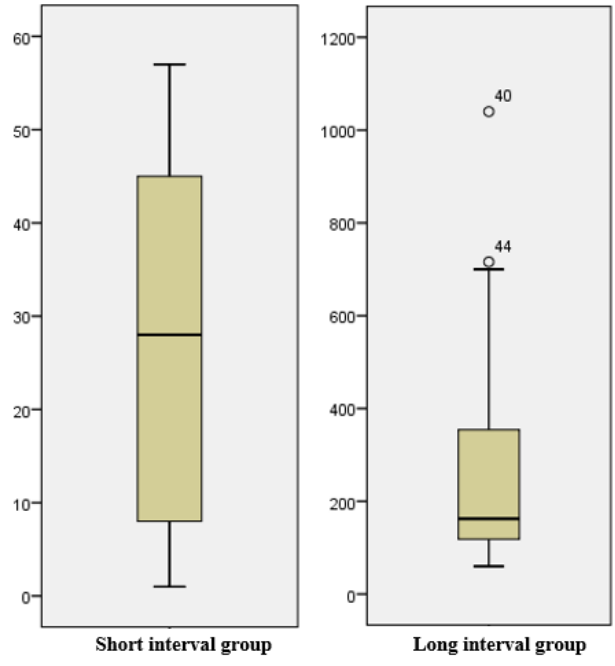


**Figure 2.** Boxplot of time interval (days) from potassium serum test to ECV
*ECV: Electrical cardioversion*

**Table 1.** Demographic and clinical characteristics

| Characteristic | Short interval (n=33) | Long interval (n=32) | p-value |
|---|---|---|---|
| Interval between the K test and ECV (days) | 28.00 (19.628) | 162.50 (223.074) | 0.000 |
| Serum potassium (mmol/L) | 4.245 (0.3563) | 4.194 (0.3501) | 0.557 |
| Male sex | 20 (60.6%) | 26 (81.3%) | 0.067 |
| Age (years) | 66.88 (9.496) | 65.73 (9.478) | 0.636 |
| **Comorbidities** | | | |
| Coronary artery disease | 5 (15.2%) | 7 (21.9%) | 0.485 |
| Diabetes mellitus | 4 (12.1%) | 2 (6.3%) | 0.672 |
| Heart failure | 10 (30.3) | 4 (12.5%) | 0.081 |
| Decreased renal function (<60 mL/min/1.73 m²) | 7 (21.2%) | 7 (15.6%) | 0.562 |
| **Antiarrhythmic drugs** | | | |
| Class I | 4 (12.1%) | 4 (12.5%) | 1.000 |
| Class II | 31 (93.9%) | 29 (90.6%) | 0.672 |
| Class III | 1 (3.0%) | 1 (3.1%) | 1.000 |
| Class IV | 3 (9.1%) | 2 (6.3%) | 1.000 |
| **Antihypertensive drugs** | | | |
| ACE-inhibitor | 7 (21.2%) | 6 (18.8%) | 0.804 |
| ARB | 11 (33.3%) | 5 (15.6%) | 0.098 |
| **Diuretics** | | | |
| Potassium-sparing | 1 (3.0%) | 1 (3.1%) | 1.000 |
| Loop or thiazide | 8 (24.2%) | 3 (9.4%) | 0.110 |

*Continuous variables are presented as means and standard deviations. Categorical variables are presented as counts and percentages. P-values were calculated using the chi-squared test, Fisher's exact test, Mann-Whitney U test, or independent samples t-test. Antiarrhythmic drug classes are based on the Vaughan-Williams classification system*
*ECV: Elective electrical cardioversion, K: Potassium, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker*

## Discussion

In this study, patients who had undergone potassium testing in the past did not exhibit a different risk of developing ventricular arrhythmias compared with those who had the test closer to the ECV. Second, the timing of potassium testing did not influence the success rates of the two groups.

No ventricular arrhythmias as complications following ECV were observed. This finding, which indicated the rarity of ventricular arrhythmic complications, was consistent with that presented in previously performed studies[10,11]. In a large retrospective multicenter study performed by Grönberg et al.[2] 6906 ECVs for acute AF were evaluated for immediate arrhythmic complications. No ventricular arrhythmias requiring intervention were detected, and the authors concluded that arrhythmic complications following ECV are essentially bradyarrhythmia[12]. However, Gallagher et al.[10] studied 2522 ECVs and found 5 cases of VF and 1 case of VT. Of particular interest is that the authors stated that probably all 5 cases of VF were caused by the delivery of an unsynchronized shock. Consequently, these two studies indicate that ventricular arrhythmias as a result of ECV are very rare and are most likely caused by the delivery of unsynchronized shocks.

Regarding the secondary outcomes, no differences in success rates were observed. One limitation of this outcome is that because of the retrospective nature of this study, important predictive factors for success rates, such as thoracic impedance and left atrial size[13], could not be taken into account, as these factors are often not

documented in the EHR. Kyo et al.[13] conducted a study examining success rates after 5 min of ECV in patients with new-onset AF in the intensive care unit. They found that a serum potassium level >3.8 mmol/L at the time of ECV was associated with successful ECV (odds ratio 3.13 95% confidence interval, 1.07-9.11; p=0.04)[14]. Moreover, another study demonstrated that patients who were administered an intravenous potassium and magnesium injection prior to ECV achieved successful restoration of SR significantly more frequently[6]. These findings suggest a positive correlation between higher serum potassium levels and ECV success rates. In our study, however, we did not determine the serum potassium level at the time of ECV.

The primary notion underlying this study was that patients who underwent serum potassium testing more recently would provide physicians with an opportunity to restore potassium imbalances prior to ECV, thereby potentially improving patient outcomes. In our study, however, only three patients experienced mild potassium disturbance, and all three patients belonged to the long-interval group. This outcome implies that our hypothesis may not have been fully tested because no potassium disturbances were noted or corrected in the short-interval group.

Although we did not know serum potassium levels at the time of ECV were unknown, we did analyze specific risk factors, including impaired renal function, the use of diuretics, ARBs, and ACE inhibitors, which are known to contribute to potassium disturbances. However, when comparing patients with these risk factors with those without, we did not observe any statistically significant differences in success rates. Therefore, in our study population, the risk factors for potassium disturbance did not translate into varying ECV success rates.

### Study Limitations

Furthermore, this study has several limitations. First, to divide patients into two groups, we used the median time (in days) from potassium serum test to ECV. The designation of "short interval" patients was based on this median. In a different hospital population, the median could vary, potentially leading to different results. Moreover, the "short interval" group still had a large range of approximately 2 months, during which potassium disturbances could still have occurred after the potassium serum test. This study was also limited by its small, single-center design. We exclusively enrolled outpatients undergoing elective ECV. Hospitalized patients experience potassium disturbances more frequently and may have a higher risk of adverse outcomes[15].

In the light of the growing demand for healthcare services in the Netherlands, efficient and evidence-based healthcare practices are crucial. It is crucial that tests are conducted only when valuable information is provided.

## Conclusion

In this study, we investigated the timing of potassium serum testing before ECV testing in relation to ventricular arrhythmic complications and success rates. Our findings suggest that, for patients undergoing elective ECV, routine potassium serum testing shortly before ECV has no compelling argument in terms of ventricular arrhythmic complications and success rates. Given this study's limitations, especially its small sample size, further larger-scale research is needed to validate our findings.

### Ethics

**Ethics Committee Approval:** Due to the retrospective nature of the study, ethics committee/IRB approval was waived. However, informed consent from the patient was received according to the ethical principles of the Declaration of Helsinki. The study was assessed by the Local Ethics Committee and registered in the context of transparency.

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

### Authorship Contributions

Surgical and Medical Practices: Elders J, Concept: Elders J, Design: Elders J, Broekhoven V, Data Collection

and/or Processing: Broekhoven V, Analysis and/or Interpretation: Elders J, Broekhoven V, Remmen J, Cramer M-J, Literature Search: Elders J, Broekhoven V, Writing: Elders J, Broekhoven V.

**Conflict of Interest:** The authors declare no conflicts of interest concerning the authorship or publication of this article.

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# Demographic, Clinical and Echocardiographic Characteristics of Patients with Rheumatic Mitral Stenosis Treated with Mitral Balloon Valvuloplasty Procedure: A Local Experince

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## Abstract

**Objectives:** Rheumatic mitral stenosis (RMS) remains a significant health challenge, particularly in low- and middle-income countries, due to limited access to preventive measures and timely treatment. Percutaneous mitral balloon valvuloplasty (PMBV) has become the preferred treatment for RMS, offering a less invasive alternative to surgical mitral valve replacement. This study aimed to evaluate the demographic, clinical, and echocardiographic characteristics of patients with RMS undergoing PMBV and to assess the procedural outcomes.

**Materials and Methods:** This study included 52 patients who underwent PMBV RMS. Patients with non-RMS, incomplete patient files, or previous valve surgeries were excluded.

**Results:** The procedural success rate was 87%, with better outcomes observed in patients with a Wilkins score ≤8 than in those with a score >8. PMBV resulted in a significant increase in mitral valve area (MVA) (from 1.18±0.19 cm² to 2.27±0.48 cm², p=0.001) and a decrease in both mean mitral valve gradient (from 12.82±3.5 mmHg to 5.97±2.04 mmHg, p=0.001) and maximum mitral valve gradient (from 27.12±14.0 mmHg to 12.70±3.1 mmHg, p=0.001). Although the

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## Abstract

procedure was generally safe, manageable complications, such as chordal rupture (1 case, 1.9%) and mitral regurgitation (MR) progression, were observed, particularly in patients with higher Wilkins scores.

**Conclusion:** The significant improvements in MVA and reduced gradient observed in our study underscore the effectiveness of PMBV, even in patients with higher Wilkins scores. Although we observed manageable complications, such as chordal rupture and MR progression, the overall safety and efficacy of PMBV in our patient population highlight its value as a practical and effective treatment option for RMS in our clinical setting. These findings support the continued use of PMBV as a standard treatment approach in our region, potentially enhancing the quality of care for patients with this condition.

**Keywords:** Balloon valvuloplasty, gradient mitral, stenosis, percutaneous, rheumatic, Wilkins scores

## Introduction

It remains a major challenge for global health that the burden of rheumatic heart disease (RHD) persists, especially in low- and middle-income countries where access to preventive measures and timely treatment is often limited. The severe morbidity and mortality of this disease, which affects millions of people worldwide, are due to complications arising from acute rheumatic fever. Among its various manifestations, rheumatic mitral stenosis (RMS) is particularly significant because of its potential to impair cardiac function, leading to congestive heart failure, atrial fibrillation (AF), and other life-threatening conditions[1,2].

Percutaneous mitral balloon valvuloplasty (PMBV) has become the cornerstone treatment of choice for RMS, offering a less invasive alternative to surgical valve replacement. It not only alleviates symptoms associated with mitral valve obstruction but also improves overall patient outcomes[3,4]. Given the dynamic epidemiology of RHD and evolving therapeutic modalities, extensive research on the long-term outcomes and efficacy of PMBV in patients with RMS is warranted. Understanding the characteristics of these patients and the success rates of these procedures is critical for optimizing treatment strategies and improving the quality of care provided to these patients[5,6].

To bridge the existing knowledge gap, our study aims to provide detailed information on these issues by conducting a comprehensive evaluation of individuals diagnosed with RMS who have undergone PMBV in our cardiology clinic. This research not only provides insight into patient outcomes after PMBV but also elucidates the long-term effects of PMBV in our regional setting[7,8].

Our research aims to analyze the demographic, clinical, and echocardiographic features of this patient group and to study their post-valvuloplasty outcomes. The findings will hopefully contribute significantly to the understanding of this condition, guiding clinical practice and laying the groundwork for future research on improved therapeutic strategies for RMS[9]. Furthermore, by identifying prevalent risk factors and patient profiles most likely to benefit from PMBV, the study will help develop individualized treatment plans that address the specific needs of these patients[10].

In summary, RMS, which is characterized by significant morbidity and mortality, urgently requires research focusing on management approaches, such as PMBV. Therefore, based on a comprehensive analysis of patient records, our study contributes to a better understanding of the outcomes associated with treatment interventions in RMS, thereby enabling improvements in healthcare and medical practice.

## Materials and Methods

This retrospective study was conducted at our cardiology clinic. The medical history and demographic characteristics of the patients were obtained from the hospital data. Transesophageal echocardiography (TEE) was performed in all patients before the procedure. Patients with an asymptomatic valve area greater than 1.5 cm², moderate to severe mitral regurgitation (MR) (3+, 4+), other valvular pathologies or coronary artery disease requiring surgery, left atrial thrombus seen through TEE, or a Wilkins score >12 were excluded.

From an initial cohort of 63 patients with symptomatic RMS evaluated for PMBV, 9 patients were excluded due to the following contraindications: mitral valve area (MVA) >1.5 cm²; moderate or severe MR; extensive calcification of both commissures; absence of commissural fusion; significant aortic and tricuspid valve disease requiring surgery; or concurrent coronary artery disease requiring coronary artery bypass grafting. Additionally, two more patients were excluded from the analysis due to missing or unreliable data, resulting in a final sample size of 52 subjects (Figure 1).

**Echocardiography:** Echocardiography was performed with a Vivid S6 echocardiography machine (GE-Vingmed Ultrasound, Horten, Norway) using 2.5 MHz transthoracic and 6 MHz transesophageal probes, according to the American Society of Echocardiography guidelines. Different measurements were performed three times to enhance the accuracy. Parasternal long-axis views, apical four-chamber views, and M-mode 2-D echo Doppler were taken into consideration for evaluation. Pulsed-wave Doppler analysis was also employed in conjunction with continuous-wave Doppler methods. The other methods used include planimetry for measuring MVA and pressure half-time techniques. The morphological characteristics of the mitral valve were classified using the Wilkins scoring system, ranging from 1 to 16 points, with patients scoring ≤12 considered suitable for the procedure.

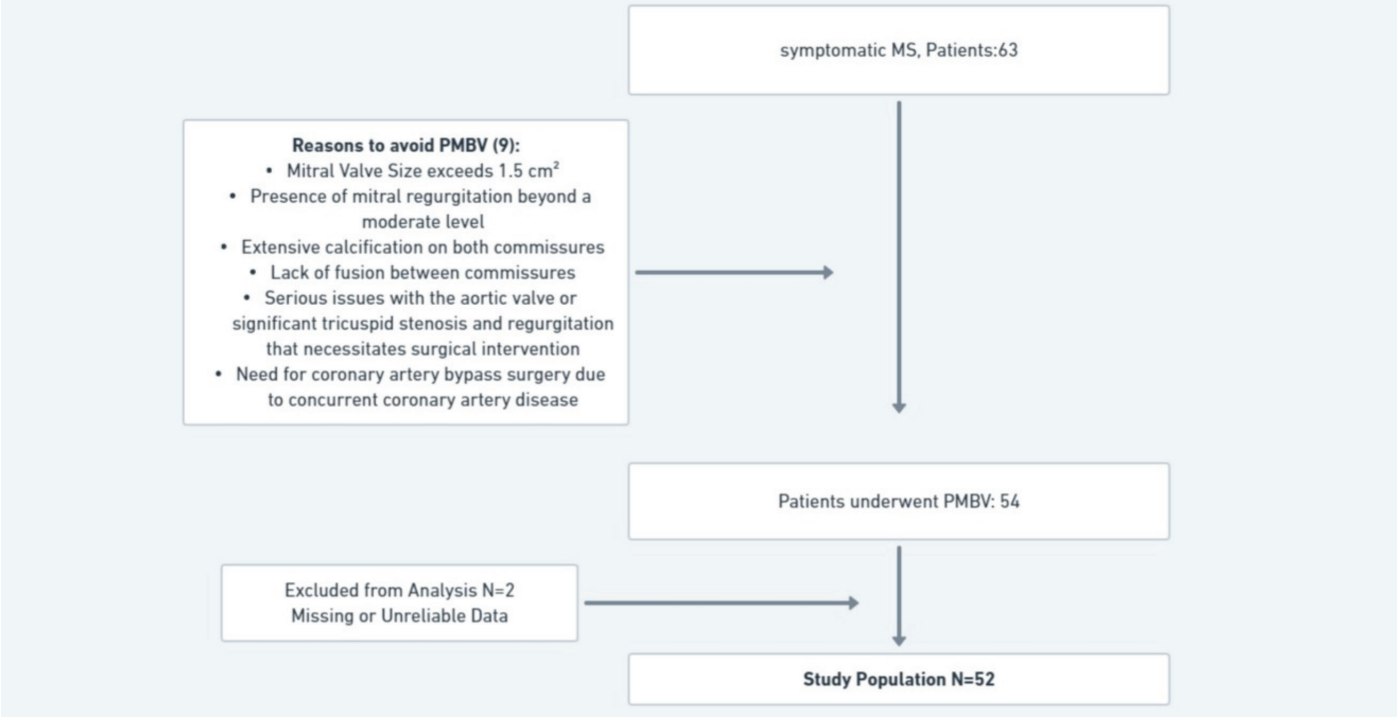


**Figure 1.** Study design

*PMBV: Percutaneous mitral balloon valvuloplasty, MS: Mitral stenosis*

All patients underwent TEE before the operation to exclude left atrial thrombus, evaluate mitral valve morphology and regurgitation, and establish other major cardiac pathologies.

**PMBV:** PMBV was performed under local anesthesia using a trans-septal approach through the right femoral vein. TTE monitoring was performed during and after the procedure. Hemodynamic measurements were performed intraoperatively. The Inoue balloon system (Toray Industries Inc, Tokyo, Japan) was used throughout the experiment, and the balloon size was determined at the discretion of the operator. The procedure was terminated if a commissural tear, significant increase in mitral valve area, significant decrease in mitral valve gradient, or the development of moderate-to-severe MR was detected during the procedure. Procedural success was defined as a 50% increase in MVA compared with the pre-procedural value and/or an (MVA) >1.5 cm², with no development of MR grade 3+ or 4+.

**Follow-up:** Clinical follow-up and echocardiographic evaluation were performed before the intervention, within 24-48 hours after the intervention, at 3-6-month intervals, and then annually thereafter. Successful endpoints were defined similarly to procedural success criteria, with respect to significant improvement in MVA without the appearance of severe MRs.

### Statistical Analysis

Statistical analysis was performed using SPSS software. Continuous variables were presented as mean ± standard deviation and categorical variables expressed as absolute frequencies (n) or percentages (%). Trend analysis used the Cochran-Armitage test, with a significance level set at $p<0.05$.

This methodological approach ensured a comprehensive assessment of the PMBV results, adhering to ethical standards, and ethics committee approval was obtained from the Van Yüzüncü Yıl Non-Interventional Clinical Research Ethics Committee (approval no.: 2019/10/11 date: 24.05.2019). Informed consent was obtained from all participants, ensuring their voluntary participation and confidentiality.

## Results

Our research enrolled 52 consecutive patients (36 females, 16 males; mean age 48±13 years; range 24 to 76 years, Table 1) who underwent PMBV for symptomatic RMS with a valve area ≤1.5 cm². The procedural success rate was 87%, which was higher in patients with a Wilkins score ≤8 (90%) than in those with a Wilkins score >8 (80%). Of the 7 unsuccessful procedures, 3 were in subjects with low Wilkins scores, and 4 were in subjects with high Wilkins scores. Furthermore, there were 8 patients with AF, with 2 in the Wilkins ≤8 group and 6 in the Wilkins >8 group, indicating that older individuals might be more susceptible to AF, possibly leading to increased AF among patients with a Wilkins score >8 (p=0.001) (Table 2). The distribution of study subjects into different New York Heart Association classes revealed significant diversity in preprocedural functional status, reflecting the echocardiographic and demographic variations observed between the Wilkins score groups. Notably, the left ventricular internal diameter at end-diastole (LVIDd) was significantly larger in the Wilkins >8 group (5.35±0.85 cm) than in the Wilkins ≤8 group (4.93±0.52 cm) (p=0.035), and the left atrium (LA) size was also greater in the Wilkins >8 group (4.82±0.63 cm) than in the Wilkins ≤8 group (4.44±0.51 cm) (p=0.025). Additionally, the left atrial area was significantly larger in patients with a Wilkins score >8 (30±5.74 cm²) compared to those with a Wilkins score ≤8 (25.37±4.36 cm²) (p=0.001) (Table 2).

Baseline demographic and echocardiographic characteristics before RMS revealed important insights into the structural heart changes associated with RMS in this population. The study population was divided according to the previously mentioned PMBV determinant, Wilkins score. The left ventricular ejection fraction for those with a lower score of ≤8 was 64.88±3.34% compared to 62.90±4.86% in the Wilkins

score >8 subgroup, with no statistical difference between them (p=0.89). However, significant differences in LVIDd were observed between patients with a Wilkins score >8 (5.35±0.85 cm) and those with a Wilkins score ≤8 (4.93±0.52 cm), indicating severe dilatation (p=0.035). Furthermore, the larger LA size in the Wilkins score ≤8 group was smaller than that in the Wilkins score >8 group, suggesting that long-standing MR alters the geometry of the atria over time (p=0.025)[10]. These differences in baseline characteristics reflect the higher echocardiographic burden in patients with higher Wilkins scores, which calls for a more thorough preprocedural evaluation to predict PMBV outcomes (Table 2).

Post-procedure TTE measurements, as shown in Table 3, clearly demonstrate the effectiveness of PMBV in our study cohort. The procedure resulted in a significant increase in MVA from 1.18±0.19 cm² before to 2.27±0.48 cm² after PMBV in all subjects treated (p=0.001). This change was consistent and significant between the two groups: Wilkins score ≤8 and Wilkins score >8, thereby confirming the broad efficacy of PMBV. More specifically, MVA increased significantly from 1.26±0.16 cm² to 2.47±0.43 cm² in those with scores ≤8, and from 1.05±0.16 cm² to 1.95±0.35 cm² in those with scores >8[11].

Furthermore, the mean gradient (MeanG) and maximum gradient (MaxG) through the mitral valve

**Table 1.** Preoperative characteristics of patients in terms of age and functional capacity

| Parameter | n | Total (Mean±SD) | Wilkins ≤8 (n=32) (Mean±SD) | Wilkins >8 (n=20) (Mean±SD) |
|---|---|---|---|---|
| Gender | 52 | 48±13 | 40±10 | 61±8 |
| Male | 16 | 53±11 | 44±10 | 61±15 |
| Female | 36 | 46±14 | 38±23 | 62±10 |
| NYHA class I | 0 | - | - | - |
| NYHA class II | 20 | - | 18 | 2 |
| NYHA class III | 27 | - | 12 | 15 |
| NYHA class IV | 5 | - | 2 | 3 |

*NYHA: New York Heart Association, SD: Standard deviation*

**Table 2.** Preoperative baseline echocardiographic and demographic characteristics of patients

| Parameter | Wilkins ≤8 (n=32) | Wilkins >8 (n=20) | p-value |
|---|---|---|---|
| LVEF | 64.88±3.34 | 62.90±4.86 | 0.89 |
| LVIDd | 4.93±0.52 | 5.35±0.85 | 0.035 |
| LVIDs | 3.92±0.44 | 4.00±0.59 | 0.565 |
| LA | 4.44±0.51 | 4.82±0.63 | 0.025 |
| LAarea | 25.37±4.36 | 30±5.74 | 0.001 |
| sPAB | 49.25±7.26 | 48.7±9.10 | 0.811 |
| HR | 85±10 | 83±12 | 0.511 |
| AF | 2 | 6 | 0.001 |
| HT | 4 | 3 | - |
| DM | 4 | 4 | - |
| Coronary artery disease | 2 | 3 | - |
| Smoking | 11 | 5 | - |
| Cerebrovascular events | 0 | 1 | - |
| Pregnancy | 2 | 0 | - |

*LVEF: Left ventricular ejection fraction, LVIDd: Left ventricular internal diameter at end-diastole, LA: Left atrium, LAarea: Left atrial area, sPAB: Systolic pulmonary artery pressure, HR: Heart rate, AF: Atrial fibrillation, HT: Hypertension, DM: Diabetes mellitus*

decreased considerably, suggesting a post-PMBV improvement in blood flow and reduction in cardiac workload[12]. After the procedure, significant decreases in pulmonary hypertension were observed, indicating that PMBV can be successfully used to correct RMS regardless of the initial Wilkins score, leading to better clinical outcomes and improved quality of life for these patients (Table 3).

Comparative laboratory values before and after PMBV treatment demonstrate the systemic effects of this cardiac intervention. The total white blood cells (WBC) count slightly decreased from 7913±2186 cells/µL to 7528±2588 cells/µL, indicating a non-significant systemic inflammatory response following PMBV. Consequently, total neutrophil counts within the WBC decreased from 4940±2012 to 4589±2053. There were minimal variations in lymphocyte counts, implying that the procedure had an insignificant effect on systemic inflammation. The relationship between these two types of blood cells remained relatively stable, indicating no significant effect on overall health after surgery. The serum levels of C-reactive protein and creatinine remained stable, indicating that systemic safety was not affected by the procedure. Thyroid stimulating hormone (TSH) levels did not change after PMBV, indicating normal thyroid function. Overall, these findings demonstrated the procedural safety of PMBV without significant systemic inflammatory markers or organ dysfunction (Table 4).

Our research aimed to identify hospital situations and outcomes during 1-month follow-up after PMBV. The primary objective of this study was to evaluate treatment outcomes and safety measures with respect to certain conditions that occur while patients are still hospitalized or during the first 4 weeks after the PMBV procedure. Data from each patient was recorded using a data collection form designed by the researcher. A total of 52 patients were included in the analysis; they were stratified into two groups based on Wilkins scores: ≤8 (32 patients) and >8 (20 patients). There was an increase in MR in one patient per group, which may indicate a potential worsening of

**Table 3.** Changes in echocardiographic parameters before and after PMBV

| Parameter | Pre PMBV (Total) | Post PMBV (Total) | p-value | Pre PMBV Wilkins ≤8 | Post PMBV Wilkins ≤8 | Pre PMBV Wilkins >8 | Post PMBV Wilkins >8 | p-value |
|---|---|---|---|---|---|---|---|---|
| MVA, cm² (planimetric) | 1.18±0.19 | 2.27±0.48 | 0.001 | 1.26±0.16 | 2.47±0.43 | 1.05±0.16 | 1.95±0.35 | 0.001 |
| MeanG, mmHg | 12.82±3.5 | 5.97±2.04 | 0.001 | 12.87±4.0 | 5.82±2.04 | 12.73±2.9 | 6.20±1.72 | 0.521 |
| MaxG, mmHg | 27.12±14.0 | 12.70±3.1 | 0.001 | 28.25±18.19 | 12.16±3.43 | 25.32±6.60 | 13.55±2.57 | 0.127 |
| PHT (cm²) | 1.18±0.19 | 2.26±0.44 | 0.001 | 1.25±0.16 | 2.43±0.42 | 1.07±0.19 | 1.98±0.33 | 0.01 |
| sPAB (mmHg) | 49±8 | 33±11 | 0.001 | 48±9 | 32±9 | 50±7 | 35±12 | 0.811 |

*PMBV: Percutaneous mitral balloon valvuloplasty, MVA: Mitral valve area, MeanG: Mean gradient, MaxG: Maximum gradient, PHT: Pulmonary hypertension, sPAB: Systolic pulmonary artery pressure*

**Table 4.** Changes in laboratory values before and after PMBV

| Parameter | Pre-procedure | Post-procedure | p-value |
|---|---|---|---|
| WBC (cells/µL) | 7913±2186 | 7528±2588 | p>0.05 |
| Neutrophil (cells/µL) | 4940±2012 | 4589±2053 | p>0.05 |
| Lymphocyte (cells/µL) | 20145±724 | 2292±868 | p>0.05 |
| N/L ratio | 2.56±1.42 | 2.6±2.37 | p>0.05 |
| CRP (mg/L) | 8.22±11.26 | 16.08±35.198 | p>0.05 |
| Creatinine (mg/dL) | 0.80±0.16 | 0.82±0.19 | p>0.05 |
| TSH (µIU/mL) | 5.19±16.23 | 5.27±12.68 | p>0.05 |

*PMBV: Percutaneous mitral balloon valvuloplasty, WBC: White blood cells, CRP: C-reactive protein, TSH: Thyroid stimulating hormone, N: Neutrophils, L: Lymphocyte*

valve function after PMBV. During follow-up, three mitral valve replacements were performed, all in the higher Wilkins score category, highlighting the increased procedural difficulty and risk in patients with severe mitral stenosis (MS). Minor complications, such as groin hematomas, were evenly distributed between the groups, without any major adverse cardiovascular events, strokes, or procedure-related deaths, indicating the overall safety and effectiveness of PMBV in these patients (Table 5).

The results of our investigation clearly indicate the safety and efficacy of PMBV as a treatment option for patients with RMS. PMBV improved MVA in various categories of patients with different levels of disease severity, according to their Wilkins scores, with a success rate of up to 87%. Significantly, the intervention led to considerable reductions in both MeanG and MaxG across the mitral valve, indicating decreased cardiac workload and improved blood flow. The stability of laboratory values after the procedure further signifies minimal systemic impact, demonstrating PMBV's safety from this perspective. Although some manageable complications did arise, it should be emphasized that no major adverse events, including procedure-related deaths, were recorded, thus proving PMBV's validity as an alternative method for managing RMS. These findings suggest that PMBV could be used as a standard treatment for patients with RMS, opening the door to further research and wider clinical application.

## Discussion

The results of this study support the use of PMBV as a highly effective and safe method for treating RMS. This procedure significantly improves echocardiographic parameters and has high procedural success rates. Stable laboratory values after PMBV indicate that the procedure is less invasive than surgery, thereby ensuring safety and alleviating concerns about potential systemic complications. The serum levels of C-reactive protein and creatinine remained stable, indicating that systemic safety was not affected by the procedure. TSH levels did not change after PMBV, indicating normal thyroid function. The findings of this study demonstrate PMBV safety profile, given the absence of major adverse events and the manageable nature of the observed complications. This makes PMBV a compelling option for both physicians and patients, emphasizing its role in improving patient outcomes and quality of life for patients with RMS[12,13].

Research on PMBV in patients with RMS demonstrated high efficacy and safety, with significant improvements in MVA and reductions in mean and maximum mitral valve gradients across different Wilkins score categories.

**Table 5.** In-hospital and short-term follow-up events

| Parameter | Total | Wilkins ≤8 | Wilkins >8 |
|---|---|---|---|
| Number of patients | 52 | 32 | 20 |
| Chordal rupture | 1 | - | 1 |
| Emergency MVR | 1 | - | 1 |
| Advanced MR | 2 | 1 | 1 |
| Total MVR (12±6 months follow-up) | 3 | - | 3 |
| Mild pericardial effusion | 2 | 1 | 1 |
| Stroke | 1 | 1 | - |
| Groin hematoma | 2 | 1 | 1 |
| Unsuccessful PMBV | 7 | 3 | 4 |
| MACE | 1 | 0 | 1 |

*MVR: Mitral valve replacement, MR: Mitral regurgitation, PMBV: Percutaneous mitral balloon valvuloplasty, MACE: Major adverse cardiac events- mitral valve replacement*

However, complications such as chordal rupture (1 case, 1.9%) and progression to higher-degree MR were observed, particularly among patients with higher Wilkins scores. These baseline differences reflect the greater echocardiographic burden in patients with higher Wilkins scores, highlighting the need for a thorough preprocedural evaluation to predict PMBV outcomes. Additionally, the occurrence of AF in 8 patients, particularly older individuals who are more susceptible, suggests an increased incidence of AF in patients with a Wilkins score >8. These findings highlight the importance of careful patient selection and monitoring during the PMBV procedure[14-16]. Our study results are consistent with those reported in other regional centers, which have similarly observed high procedural success rates and significant improvements in the mitral valve area. The uniformity of outcomes across different Wilkins score echelons indicates broad applicability of the procedure. However, our study also identified manageable complications, especially among patients with higher Wilkins scores, which is consistent with the experiences of other centers in the region[17-19].

Our study reaffirms that PMBV is an effective and safe treatment for RMS, with results closely aligning with those of local studies by Yuce et al.[20], Korkmaz et al.[21] and Yıldız[22]. We observed significant improvements in MVA and a reduction in transmitral gradients, consistent with the findings of Yuce et al.[20], who reported increases in MVA and symptom relief. Similarly, Korkmaz et al.[21] and Yıldız[22] also demonstrated effective gradient reduction and improved pulmonary pressures. Our study showed a low complication rate, which matches the findings of Yuce et al.[20], who noted only a small increase in severe mitral regurgitation. Korkmaz et al.[21] and Yıldız[22] also reported low complication rates, emphasizing the importance of operator skill in ensuring safety. We observed sustained improvements in MVA and patient function with few re-interventions. This echoes the durability of the results reported by Yuce et al.[20] with similar long-term benefits noted in the studies by Korkmaz et al.[21] and Yıldız[22].

The minimal systemic impact of PMBV, as indicated by stable laboratory values, echoes findings from other studies that emphasize the safety of PMBV. However, the occurrence of complications in patients with higher Wilkins scores highlights the need for further research to refine the PMBV technique. Future studies should explore alternative approaches, such as balloon size adjustments or targeted interventions for specific mitral valve morphologies, to reduce the risk of complications[23-25]. The results of our investigations indicate the safety and efficiency of PMBV as a treatment option for patients with RMS. PMBV improved the MVA in various categories of patients, corresponding to different levels of disease severity according to their Wilkins score, with a success rate of up to 87%.

### Study Limitations

While our study provides valuable insights, it is important to note its limitations, particularly its retrospective observational design, which may have introduced selection bias. Additionally, the concentration of this research in a single facility may limit the generalizability of the findings to other populations. Future multicenter, prospective studies are needed to validate these findings and ensure their broad applicability[26-29]. Consistency of our findings with those of these local studies highlights the reliability of PMBV. Despite some variations, the high success rates and safety profiles underscore the procedure's value as a standard treatment for RMS.

## Conclusion

The study was specifically conducted to mitigate this condition by opening up the heart valves of 52 people who had contracted rheumatic fever and were diagnosed with severe MS. The study reported a procedural success rate of 87% in patients with RMS, showing significant improvements in mitral valve areas and gradients post-procedure. PMBV was also effective in patients with high Wilkins scores, leading to hemodynamic and symptomatic recovery. However, complications, such

as chordal rupture and MR progression, were observed in patients with higher Wilkins scores. Although these complications were manageable, the overall safety and efficacy of PMBV were underscored. The research results advocate for the use of PMBV as an appropriate alternative to surgery because PMBV is practical, low-risk, cost-effective, and efficient for improving hemodynamic and symptomatic outcomes among post-procedure patients with RMS.

### Ethics

**Ethics Committee Approval:** Ethics Committee approval was obtained from the Van Yüzüncü Yıl Non-Interventional Clinical Research Ethics Committee (approval no.: 2019/10/11 date: 24.05.2019).

**Informed Consent:** Informed consent was obtained from all participants, ensuring their voluntary participation and confidentiality.

### Authorship Contributions

Surgical and Medical Practices: Tüner H, Kaya Y, Concept: Tuncer M, Design: Tüner H, Kaya Y, Data Collection and/or Processing: Tüner H, Analysis and/or Interpretation: Tüner H, Tuncer M, Literature Search: Tüner H, Tuncer M, Writing: Tüner H.

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# Relationship Between Exercise Electrocardiography Findings and Cardiovascular Events and the Extent of Coronary Artery Disease: What is New?

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## Abstract

**Objectives:** The exercise treadmill test (ETT) is commonly used in cardiology practice. Detection of the severity of coronary artery disease (CAD) by the surrogates of ETT is of great importance to guide the management plan. Here, we aimed to identify the best ETT surrogates to detect the extent of CAD and major adverse cardiovascular events (MACE) during follow-up.

**Materials and Methods:** This retrospective study included patients with positive ETT results for coronary ischemia who underwent invasive coronary angiography after the index ETT. The following surrogates of ETT were used in the study for the analyses: exercise duration; maximum workload achieved in METS; rate-pressure product (RPP) at rest, at peak, and at 3rd minute in the recovery; number of leads with ST deviation; and Duke treadmill score (DTS). Patients were classified into low-risk, intermediate-risk, and high-risk groups according to the SYNTAX score. The ETT findings of the groups were compared.

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**Results:** The study included 48 patients: low-risk group: 24 (50%); intermediate-risk group: 10 (21%); and high-risk group: 14 (21%). The average age was 50±8 years. DTS, peak RPP, recovery RPP, and number of leads with ST deviation were significantly different between the high-risk group and the other groups. These variables were well correlated with the SYNTAX score, presence of the left main coronary artery (LMCA) lesion, and development of MACE at follow-up.

**Conclusion:** DTS, peak RPP, recovery RPP, and number of leads with ST deviation are well correlated with the extent of CAD, presence of LMCA lesions, and development of MACE at follow-up.

**Keywords:** Coronary artery disease, exercise treadmill test, Duke treadmill score, rate-pressure product, SYNTAX score

## Introduction

Chest pain or its equivalent is the most frequently occurring cardiac symptom[1]. Evaluation in an emergency or office setting is performed with the help of non-invasive stress modalities such as the exercise treadmill test (ETT), stress echocardiography, and myocardial perfusion scintigraphy[1,2].

The ETT is the most commonly used and first-step diagnostic tool in the assessment of chest pain or other cardiac symptoms in patients with low to intermediate 10-year cardiovascular risk[3]. Because of its low cost and widespread availability, ETT is commonly recommended for patients presenting with interpretable baseline electrocardiography (ECG) findings in the evaluation of chest pain or other cardiac symptoms[4]. However, its sensitivity and specificity are limited (67% and 71%, respectively) depending on the target population[1,4-6].

Improper interpretation of ETT may result in the underestimation of underlying coronary artery disease (CAD) or ignoring warning findings that may lead to false-negative results for coronary ischemia[7]. Thus, the detection of such warning findings in ETT may help guide physicians.

Although the sensitivity and specificity of the ETT vary according to the population in concern and the clinical setting in which the ETT is performed, its value in the long-term survival of patients with regard to the development of new cardiovascular events has not been studied sufficiently. Additionally, surrogates that may reflect coronary artery anatomy and long-term survival have not been studied in detail in the literature.

Duration of the ETT, the maximum workload achieved in metabolic equivalents (METs), heart rate at peak exercise and the third minute in recovery, percentage of the maximum heart rate achieved as per age-predicted target heart rate, blood pressure readings at peak exercise and the third minute in recovery, number of leads with ST deviation in positive ETT, Duke treadmill score, maximum ST deviation in millimeter in patients with positive ETT, ST deviation developed at peak exercise or recovery in patients with positive ETT, number of leads with ST deviation in positive ETT may be mentioned among these potential ETT surrogates. The establishment of such studies can improve the quality of care in institutions and can guide physicians in respect to the proper interpretation of this test in the evaluation of cardiac patients. Detecting such abnormal surrogates during ETT may help physicians take early action to achieve close follow-up or intervention.

Here, we aimed to identify the best ETT surrogates to detect the extent of CAD and major adverse cardiovascular events (MACE) during follow-up.

## Materials and Methods

This was a retrospective; non-invasive study that included patients aged between 18 and 65 years who underwent ETT between March 2015 and February 2020 in the cardiology department due to CAD assessment due to chest pain, dyspnea, and palpitation evaluation. The study included patients who were ETT positive

for coronary ischemia. All patients underwent invasive coronary angiography within six months following the index ETT. The study protocol was approved by Hamad Medical Corporation Ethical and Institutional (approval no.: MRC-01-21-279 date: 23.03.2021).

Any patient who was not able to complete ETT due to orthopedic reasons was excluded. Additionally, patients with previously diagnosed CAD, history of cardiac surgery, acute coronary syndrome before ETT, renal disease (glomerular filtration rate less than 90 mL/minute), elevated hepatic transaminase levels (more than 3 times from the upper normal limit) at baseline, concomitant moderate or severe valvular disease, wall motion abnormalities on echocardiographic examination, malignancy, hemoglobin level 10 gm/dL, and active infection at the time of ETT were excluded. Additionally, patients with a left ventricle ejection fraction (LVEF) of 50%, hypertrophic cardiomyopathy, congenital heart disease, and moderate or severe valvulopathy were not included. Additionally, patients with non-interpretable baseline ECG findings, such as left bundle-branch block, baseline ST depression, and pre-excitation were not enrolled in the study.

Age, gender, and body mass index (BMI) of each subject were recorded. BMI was calculated using a formula (weight in kg divided by square of height in meters). Concomitant morbidities, such as hypertension (the last 3 blood pressure measurements >140/90 mmHg or treatment with antihypertensive medication within the last 6 months) and diabetes mellitus (any patient under oral anti-glycemic drugs or insulin treatment or HbA1c over 7.0%), were recorded.

The presence of other cardiovascular risk factors was determined according to the following criteria: positive family history of CAD (presence of CAD in first-degree family members, male <55 years, or female <65 years), and cigarette smoking (current cigarette smoker or using tobacco products in the last 2 years).

Blood hemoglobin, creatinine, HbA1c, thyroid-stimulating hormone values, and fasting lipid profile [total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL)] at the time of ETT were obtained.

Transthoracic echocardiographic examinations (TTE) of the patients were performed on the same day as the index ETT. TTE images of all patients were reviewed, and all measurements related to interventricular septum thickness at diastole (IVSd), posterior wall thickness at diastole, left atrium (LA) volume index, LVEF, mitral flow E/mitral annulus lateral e' ratio, and grade of the left ventricle diastolic dysfunction were obtained as per the recommendations of the American Society of Echocardiography[8].

Baseline ECG data for all patients were obtained before ETT was performed to exclude patients with non-interpretable baseline ECG. All ETTs were performed as per the Bruce protocol in the same non-invasive laboratory of the same health center by the same staff who were blinded to the study protocol. ETT was considered abnormal in the development of exertional hypotension, malignant ventricular arrhythmias, or limiting chest pain during ETT. Additionally, an abnormal exercise ST response was defined as follows: 1 mm of horizontal or down-sloping ST deviation depression (80 ms after J point) or 1 mm of ST segment elevation in leads without pathological Q waves (excluding aVR lead)[2].

The following surrogates of ETT were used in the study for the analyses: duration of the exercise; maximum workload achieved in METS; heart rate at rest, at peak exercise, and at the third minute in recovery; percentage of the maximum heart rate achieved as per age-predicted target heart rate; blood pressure readings at rest, at peak exercise, and at the third minute in recovery; number of leads with ST deviation of more than 0.5 mm except lead aVR; presence of cardiac symptoms.

### Statistical Analysis

The data analyses were performed by using version 20 SPSS analysis program (Statistical Package for Social Sciences-SPSS, Inc., Chicago, lllinois) for Windows. The distribution of data was assessed using the Kolmogorov-

Smirnov test. Age, BMI, hemoglobin, creatinine, LDL, HDL, ETT duration, ETT workload in METs, maximum ST segment during ETT, rate-pressure product (RPP), Duke treadmill score (DTS), SYNTAX score, LVEF, and left ventricle end-diastolic diameter (LVEDD) values were normally distributed. Normally distributed continuous variables are presented as mean ± standard deviation, whereas non-normally distributed variables are expressed as median (interquartile range). Categorical data are presented as counts and percentages.

The Mann-Whitney U and Kruskal-Wallis tests were used to compare the difference of the groups with respect to non-normally distributed variables, whereas Student's t-test and ANOVA were used for normally distributed variables. The chi-square test was used to analyze the relationships among categorical variables of the groups if all cells had an expected frequency of >25. In the 2x2 contingency tables; the Yates (Continuity Correction) test was used when one or more of the cells had an expected frequency of 5-25, the Fisher's exact test was used when one or more of the cells had an expected frequency of 5 or less. Furthermore, in the R X C contingency tables, Fisher-Freeman-Halton test was preferred over chi-square test when one or more of the cells had an expected frequency of 5 or less. Pearson or Spearman correlations were used to perform correlation analyses as per homogenity of the variables. P values below 0.05 was considered statistically significant.

## Results

The study included 48 patients who satisfied the inclusion criteria. Of them, 5 (10.4%) patients were female. The number of patients in each group was as follows: low-risk group, 24 patients (50%); intermediate-risk group, 10 patients (21%); and high-risk group, 14 patients (21%). The average age of the study population was 50±8 years.

In comparison of the groups, there were no significant differences in age, sex, BMI, presence of diabetes mellitus, hypertension, smoking status, or family history of premature CAD (for all comparisons p>0.05) (Table 1). All laboratory results used in the study were not statistically significant in the groups (for all comparisons p>0.05) (Table 1).

**Table 1.** Demographic and laboratory findings of the groups classified as per SYNTAX score

| | Low-risk group (n=24) | Intermediate-risk group (n=10) | High-risk group (n=14) | p-value |
|---|---|---|---|---|
| Age (year) | 49±6 | 52±9 | 51±11 | 0.528 |
| Sex (female, %) | 3 (12.5) | 1 (10.0) | 1 (7.1) | 0.867 |
| BMI | 26.5 (6.75) | 27.5 (4.3) | 26.0 (6.0) | 0.985 |
| DM (%) | 9 (37.5) | 6 (60.0) | 8 (57.1) | 0.346 |
| HTN (%) | 8 (33.3) | 5 (50.0) | 9 (64.0) | 0.170 |
| Smoking status (%)<br>Smoker<br>Ex-smoker<br>Non-smoker | <br>18 (75.0)<br>5 (20.8)<br>1 (4.2) | <br>9 (90.0)<br>1 (10.0)<br>0 (0.0) | <br>11 (78.6)<br>3 (21.4)<br>0 (0.0) | 0.703 |
| Family history of premature CAD (%) | 6 (25.0) | 2 (20.0) | 4 (28.6) | 0.892 |
| Hgb (gr/dL) | 14.2±1.5 | 14.1±1.9 | 14.0±0.8 | 0.849 |
| Creatinine (mg/dL) | 78±15 | 87±20 | 86±15 | 0.242 |
| HbA1c (%) | 5.9 (1.0) | 6.5 (2.2) | 6.1 (2.3) | 0.418 |
| TSH (mIU/mL) | 1.32 (1.02) | 1.08 (1.04) | 1.31 (2.58) | 0.318 |
| Total cholesterol (mmol/L) | 3.45 (2.23) | 2.90 (3.89) | 3.80 (2.82) | 0.626 |
| LDL (mmol/L) | 2.42±1.17 | 2.28±1.65 | 2.26±0.94 | 0.911 |
| HDL (mmol/L) | 1.11±0.27 | 1.07±0.34 | 0.92±0.31 | 0.163 |

*BMI: Body mass index, DM: Diabetes mellitus, HTN: Hypertension, Hgb: Hemoglobin, CAD: Coronary artery disease, TSH: Thyroid-stimulating hormone, LDL: Low-density lipoprotein, HDL: High-density lipoprotein*

The echocardiographic examination results of the groups were similar in respect to LVEF, LVEDD, IVSd at diastole, posterior wall thickness at diastole, LA diameter, LA volume index, and mitral annulus E/e' ratio (p>0.05 for all comparisons) (Table 2). Although ETT duration, ETT workload, RPP at rest, and angina development during ETT were similar overall groups; percentage of maximum heart rate achieved, RPP at peak and recovery, maximum ST deviation, number of leads with ST deviation, and DTS differed significantly between the groups (Table 2).

The coronary angiographic findings of the groups were expressed in Table 3. The high-risk group received significantly more surgical revascularization compared with the other groups (p<0.001). The low-risk group received more percutaneous coronary intervention than the other groups (p<0.001). Although the number of MACE events was higher in the high-risk group, the difference was not statistically significant (p=0.100). Follow-up durations were similar between the groups (p=0.876).

The average percentage of maximum heart rate achieved by the high-risk group (81±10 bpm) was significantly lower than that of the low-risk group (89±10 bpm) (p=0.021) and the intermediate-risk group (90±10 bpm) (p=0.034). The high-risk group achieved significantly less RPP at peak exercise compared with the low-risk group (p<0.001) and intermediate-risk group (p<0.001). A similar relationship was found between the high-risk group versus the low-risk group (p<0.001) and the high-risk group versus the intermediate-risk group (p=0.016) concerning RPP at recovery.

Although a higher ST deviation was observed in the high-risk group compared with the intermediate group, it did not reach the level of statistical significance (p=0.178). However, a higher maximum ST deviation was observed in the high-risk group compared with the low-risk group (p<0.001). The high-risk group developed a higher number of leads with ST deviation than the low-risk group (p<0.001) however higher number of leads with ST

**Table 2.** The findings of echocardiographic examination and ETT among the groups

| | Low-risk group (n=24) | Intermediate-risk group (n=10) | High-risk group (n=14) | p-value |
|---|---|---|---|---|
| LVEF (%) | 59±3 | 58±3 | 57±4 | 0.355 |
| LVEDD (mm) | 47±3 | 46±6 | 48±3 | 0.501 |
| IVSd (mm) | 10 (2) | 9 (4) | 10 (3) | 0.679 |
| PWd (mm) | 9 (3) | 9 (3) | 10 (3) | 0.081 |
| LA diameter (mm) | 35 (7) | 34 (11) | 36 (3) | 0.842 |
| LA volume index (mL/m$^2$) | 25.5 (10.6) | 18.0 (10.8) | 24.6 (7.1) | 0.308 |
| Mitral lateral annulus E/e' ratio | 7.0 (2.2) | 9.0 (3.9) | 8.0 (2.7) | 0.394 |
| ETT duration (minute) | 7.2±2.4 | 7.4±2.5 | 5.6±2.3 | 0.092 |
| ETT workload (MET) | 8.9±2.4 | 9.1±2.3 | 7.6±2.1 | 0.171 |
| Percentage of the maximum heart rate as a function of age-predicted target heart rate (%) | 89±10 | 90±10 | 81±10 | 0.035 |
| RPP at rest (bpm*mmHg) | 9679±2121 | 11046±2367 | 10109±1731 | 0.225 |
| RPP at peak (bpm*mmHg) | 26920±4726 | 26568±3711 | 18483±4576 | 0.000 |
| RPP upon recovery (bpm*mmHg) | 15483±2579 | 14289±2538 | 11678±2314 | 0.000 |
| Angina during ETT (%) | 15 (62.5) | 5 (50.0) | 8 (57.1) | 0.792 |
| Maximum ST deviation during ETT (mm) | 1.63±1.28 | 2.40±1.28 | 3.01±0.86 | 0.004 |
| Number of leads with ST deviation | 5.5 (4.0) | 7.0 (4.0) | 9.0 (3.0) | 0.001 |
| Duke treadmill score (points) | -3.7±6.8 | -8.2±5.2 | -13.3±6.4 | 0.000 |

*ETT: Exercise treadmill test, LA: Left atrium, LVEF: Left ventricle ejection fraction, LVEDD: Left ventricle end-diastolic diameter, IVSd: Interventricular septum thickness at diastole, PWd: Posterior wall thickness at diastole, RPP: Rate-pressure product, MET: Metabolic equivalent*

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deviation was significant in respect to the low-risk group (p=0.177). DTS was significantly lower in the high-risk group than in the intermediate-risk group (p=0.047) and low-risk group (p<0.001).

In the correlation analyses, the SYNTAX score was found to be significantly correlated with DKS (r=-0.576, p<0.001), the number of leads with ST deviation (r=0.585, p<0.001), the maximum ST deviation (r=0.467, p<0.005), the percentage of maximum heart rate achieved (r=-0.371, p<0.01), RPP at peak (r=-0.491, p<0.001), and RPP at recovery (r=-0.438, p<0.005) respectively.

The study population was re-grouped as follows: the first group (normal or non-obstructive CAD); the second group [obstructive CAD without left main coronary artery (LMCA) disease], and third group (obstructive CAD with LMCA disease). The third group had statistically significantly lower DKS (p=0.002), higher SYNTAX score (p<0.001), lower ETT duration (p=0.025), lower RPP at peak (p=0.007), lower RPP at recovery (p=0.043), and higher number of leads with ST deviation compared with the second group (p=0.011) (Table 4).

Patients who developed MACE at follow-up had significantly lower DKS (-14.5±8.9 vs -6.4±6.9, p=0.012) and lower RPP at peak (19495±6895 bpm*mmHg vs 25085±5405 bpm*mmHg, p=0.026) compared with patients without MACE at follow-up.

There were 35 patients with obstructive CAD underwent revascularization either by percutaneous or surgical revascularization after the index ETT. Eight patients with obstructive CAD did not receive revascularization. There was no statistical difference between patients with obstructive coronary disease who underwent medical treatment (n=8) and patients with obstructive coronary disease undergone revascularization (n=35) in terms of SYNTAX score, DKS, ETT duration, RPP at peak, RPP at recovery, and number of leads with ST deviation or number of MACE events at follow-up (one event in medical treatment group and 5 events in revascularization group).

## Discussion

In this retrospective single-center study, we sought to identify ETT parameters that were correlated with the extent of CAD and development of MACE at follow-up. SYNTAX score, DKS, ETT duration, RPP at peak, RPP at recovery, and number of leads with ST deviation were

**Table 3.** Coronary angiographic findings, follow-up durations, and treatment modalities of the patients were expressed as appropriate in each group

| | Low-risk group (n=24) | Intermediate-risk group (n=10) | High-risk group (n=14) | p-value |
|---|---|---|---|---|
| CAG result (%) | | | | |
| Normal | 3 (12.5) | 0 (0.0) | 0 (0.0) | |
| Non-obstructive CAD | 2 (8.3) | 0 (0.0) | 0 (0.0) | |
| SVD | 9 (37.5) | 2 (20.0) | 0 (0.0) | |
| 2VD | 7 (29.2) | 4 (40.0) | 0 (0.0) | 0.000 |
| 3VD | 3 (12.5) | 2 (20.0) | 4 (28.6) | |
| LMCA disease | 0 (0.0) | 0 (0.0) | 2 (14.3) | |
| LMCA with SVD | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| LMCA with 2VD | 0 (0.0) | 2 (20.0) | 2 (14.3) | |
| LMCA with 3VD | 0 (0.0) | 0 (0.0) | 6 (42.9) | |
| SYNTAX score (points) | 7.3±5.2 | 19.1±1.4 | 28.7±4.8 | 0.000 |
| Treatment method (%) | | | | |
| Medical treatment | 9 (37.5) | 2 (20.0) | 2 (14.3) | |
| PCI | 15 (62.5) | 3 (30.0) | 2 (14.3) | 0.000 |
| CABG | 0 (0.0) | 5 (50.0) | 10 (71.4) | |
| MACE at follow-up (%) | 1 (4.2) | 1 (10.0) | 4 (28.6) | 0.100 |
| Follow-up duration (month) | 51 (37) | 46 (44) | 31 (58) | 0.876 |

*CAD: Coronary artery disease CABG: Coronary artery bypass grafting, CAG: Coronary angiography, SVD: Single-vessel disease, 2VD: Two-vessel disease, 3VD: Three-vessel disease, LMCA: Left main coronary artery, MACE: Major adverse cardiovascular event, PCI: Percutaneous coronary intervention*

**Table 4.** Comparison of study parameters among the groups classified as per CAD type

| | Non-obstructive coronary arteries (n=5) | Obstructive CAD without LMCA disease (n=31) | Obstructive CAD with LMCA disease (n=12) | p-value |
|---|---|---|---|---|
| SYNTAX score (points) | 1.8±4.0 | 13.7±7.9 | 27.6±6.0 | 0.000 |
| ETT duration (minute) | 7.7±1.6 | 7.2±2.5 | 5.3±2.2 | 0.047 |
| ETT workload (MET) | 9.2±1.5 | 8.9±2.4 | 7.3±2.0 | 0.081 |
| Percentage of the maximum heart rate as a function of age-predicted target heart rate (%) | 93±14 | 87±10 | 83±9 | 0.143 |
| RPP at peak (bpm*mmHg) | 30389±3700 | 25107±5292 | 20020±5040 | 0.001 |
| RPP upon recovery (bpm*mmHg) | 16386±1983 | 14318±3185 | 12682±1834 | 0.048 |
| Maximum ST deviation during ETT (mm) | 1.80±1.60 | 2.00±1.36 | 2.85±0.78 | 0.121 |
| Number of leads with ST | 7.0 (6.0) | 7.0 (4.0) | 8.5 (3.0) | 0.033 |
| Duke treadmill score (points) | -4.5±8.2 | -5.65±6.5 | -13.2±7.4 | 0.006 |
| MACE at follow-up (%) | 0 (0.0) | 2 (6.5) | 4 (33.3) | 0.100 |
| Follow-up duration (month) | 55 (19) | 42 (39) | 31 (52) | 0.608 |

*CAD: Coronary artery disease, ETT: Exercise treadmill test, LMCA: Left main coronary artery, MACE: Major adverse cardiovascular event, MET: Metabolic equivalent, RPP: Rate-pressure product*

found to be significantly different in patients with severe CAD, such as those with higher SYNTAX scores or those with significant LMCA disease.

The ETT is a widely used initial diagnostic tool for assessing cardiac complaints, such as chest pain, dyspnea, palpitation, or syncope. Sensitivity and specificity change according to the population concerned[9,10]. We also used ETT as an initial diagnostic tool to rule out obstructive CAD. It is particularly valuable and recommended for intermediate-risk patients to assess CAD[10,12]. Our study population also included middle-aged adults. The number of female patients is less compared to the literature due to the immigrant-based, male-dominant sociodemographic structure of the country. It may be considered not to include female patients in the study. However, we included all patients meeting the inclusion criteria to reflect our practice at our tertiary center as much as possible. Thus, it should be kept in mind that the clinical applicability of the study to female patients is limited.

The study population included only patients without a previous cardiac history and those without structural heart disease. Thus echocardiographic findings of the groups were similar. As is well known, longer ETT duration and higher ETT workload are associated with good prognosis among patients with CAD[11-13]. In our study, these parameters were statistically similar among the groups classified according to the SYNTAX score. Thus, other ETT parameters that differ significantly in the high-risk group can be assumed to be high-risk indicators. For example, RPP at peak and recovery were found to be lower in the high-risk group than in the others. These parameters have not been investigated in the literature.

The DTS is a well-known indicator of risk assessment, and it is widely used to triage patients with ETT exhibiting coronary ischemia[14,15]. DKS helps institutions develop their strategies for triaging patients to same-day admission, early outpatient appointments, or elective appointments, etc. In our study, DKS was also well correlated with the SYNTAX score, and the score was significantly higher in the high-risk group than in the other groups.

The amplitude of maximum ST deviation during ETT calculation is a part of the formula for calculating DKS[15]. Considering the similar frequencies of angina and ETT durations across the groups, the high-risk group was expected to have significantly more ST deviation. Additionally, our study detected a new parameter that

may indicate CAD severity. This is the number of leads with ST deviation. As the severity of CAD increased, the number of leads with ST deviation increased. Although the location of ST deviation on ECG tracings does not imply the location of the lesion, the number of leads with ST deviation may indicate more global ischemia in cases of extensive obstructive CAD.

In a study by Whitman and Jenkins[16] peak RPP was found to be correlated with the development of cardiovascular events with a mean follow-up of 5.3±2.6 years. However, they did not confirm their findings with the CAD status of the subjects. Additionally, they included patients regardless of their previous CAD status. As a result, the number of MACEs at follow-up was sufficient to perform multivariate analysis and further correlation analyses. In our study, we also found that the RPP peak was significantly lower in patients who developed MACE at a follow-up period of 45 (38) months. The follow-up duration and composition of the study population did not allow to produce a higher number of MACEs at follow-up, which is necessary for advanced statistical analyses. RPP at peak was significantly higher among high-risk patients, and was well correlated with the SYNTAX score.

A novel finding in the literature, we showed that RPP at the third minute of the recovery phase was also statistically higher in high-risk patients and was well correlated with the SYNTAX score.

Detection of an LMCA lesion in patients with cardiac symptoms during ETT is of great importance to guide and expedite the treatment plan of the patients[17]. In the literature, previous studies have mostly focused on electrocardiographic changes, especially lead aVR[17,18]. In our study, we excluded the aVR to determine the importance of deviations over other leads. For this purpose, the patients were re-grouped as having obstructive CAD without LMCA and obstructive CAD with LMCA disease. We found that patients with LMCA had significantly lower DKS, ETT duration, peak RPP, recovery RPP, and a higher number of leads with ST deviation. All these parameters imply the effect of global ischemia caused by LMCA-related ischemia. Large-scale studies are needed to determine threshold ETT parameter levels for detecting LMCA lesions or warning levels for indicating the presence of LMCA lesions.

### Study Limitations

This study has some limitations to be considered. First, it was a single-center study, reflecting the experience of only one center. Second, the study population was not large enough, but the relations were very strong and stronger in the case of a large-scale population. Third, the achievement of the age-predicted maximum heart rate was subject to the efforts of the patient, and this effort cannot be fully controlled. Thus, there may be an element of subjectivity between the groups that cannot be avoided. Lastly, the exact cutoff values of the ETT parameters have not been validated in large-scale studies, which is a major limitation of ETT studies. This fact is also valid for our study.

## Conclusion

In conclusion, surrogates of ETTs, such as DTS, RPP at peak, RPP at recovery, and number of leads with ST deviation, are well correlated with the extent of CAD, presence of LMCA lesions, and development of MACE at follow-up. Large-scale prospective studies are needed to determine cut-off values for these parameters to imply the severity of CAD and/or the presence of LMCA lesions.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by Hamad Medical Corporation Ethical and Institutional (approval no.: MRC-01-21-279 date: 23.03.2021).

**Informed Consent:** This retrospective study included patients with positive ETT results for coronary ischemia who underwent invasive coronary angiography after the index ETT.

## Authorship Contributions

Surgical and Medical Practices: Ede H, Ahmed HSS, Mahfouz AS, Bedardeen UK, Manoher G, Raja SA, Choyimadathil A, Al Okka LS, Damodharan PP, Al-Hashemi MA, Al-Qahtani AAR, Asaad NA, Concept: Ede H, Ahmed HSS, Mahfouz AS, Bedardeen UK, Manoher G, Raja SA, Choyimadathil A, Al Okka LS, Damodharan PP, Design: Ede H, Ahmed HSS, Mahfouz AS, Bedardeen UK, Manoher G, Raja SA, Choyimadathil A, Al Okka LS, Damodharan PP, Data Collection and/or Processing: Ede H, Ahmed HSS, Mahfouz AS, Bedardeen UK, Manoher G, Raja SA, Choyimadathil A, Al Okka LS, Damodharan PP, Al-Hashemi MA, Al-Qahtani AAR, Asaad NA, Analysis and/or Interpretation: Ede H, Ahmed HSS, Mahfouz AS, Bedardeen UK, Manoher G, Raja SA, Choyimadathil A, Al Okka LS, Damodharan PP, Al-Hashemi MA, Al-Qahtani AAR, Asaad NA, Literature Search: Ede H, Ahmed HSS, Mahfouz AS, Bedardeen UK, Manoher G, Raja SA, Choyimadathil A, Al Okka LS, Damodharan PP, Al-Hashemi MA, Al-Qahtani AAR, Asaad NA, Writing: Ede H, Ahmed HSS, Mahfouz AS, Bedardeen UK, Manoher G, Raja SA, Choyimadathil A, Al Okka LS, Damodharan PP, Al-Hashemi MA, Al-Qahtani AAR, Asaad NA.

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Case Report

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# Surgical Treatment of *Enterococcus Faecalis* Mitral Valve Endocarditis Complicated with Mycotic Aneurysm

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## Abstract

*Enterococcus faecalis* is a Gram-positive bacterium that can cause rapidly progressive endocarditis and requires urgent and aggressive treatment, including surgical intervention. Bacterial endocarditis may present itself with complications. Care should be taken when interpreting the differential diagnosis. In this article, we present a case of *Enterococcus faecalis* mitral valve endocarditis accompanied by subarachnoid hemorrhage and mycotic intracranial aneurysms, which are very rarely observed in the literature.

**Keywords:** Infective endocarditis, mycotic aneurysm, enterococcus faecalis, mitral valve replacement.

## Introduction

*Enterococcus faecalis (E. faecalis)* is a Gram-positive bacterium that can cause a wide range of neurological diseases, such as ischemic and hemorrhagic strokes, cerebral abscesses, mycotic aneurysms, meningitis, and encephalopathy[1]. Infective endocarditis (IE) due to *E. faecalis* is acute, can cause valve destruction, and is often fatal. IE due to *E. faecalis* may require urgent and aggressive treatment, including surgical intervention. In this study, we present a case of *E. faecalis* mitral valve endocarditis accompanied by subarachnoid hemorrhage and mycotic intracranial aneurysms, which are rarely documented in the literature. A patient with *E. faecalis* mitral valve endocarditis may initially present to the emergency department due to neurological complications.

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It is crucial to exercise careful consideration in the differential diagnosis.

## Case Presentation

A 61-year-old male patient was admitted to the emergency department with complaints of persistent weakness, fever, weight loss, and sudden collapse. An increase in body temperature, C-reactive protein, and white blood cell counts was observed. Computed tomography angiography (CTA) revealed a subarachnoid hemorrhage. Multiple small aneurysms (<2-3 mm) were identified in the right middle cerebral artery (MCA), including saccular and fusiform types in the M2 distal and M3 areas, and fusiform aneurysms in the left MCA M2 distal area. Neurosurgical consultation was performed, and surgical intervention was recommended. The patient was admitted to the neurosurgical intensive care unit and evaluated by an infectious disease specialist. Cerebrospinal fluid and blood samples were collected, and empiric parenteral antibiotics were initiated for suspected meningitis. The patient underwent emergency surgery by a neurosurgical team. The blood in the subarachnoid space was evacuated, and the aneurysms responsible for the hemorrhage were successfully controlled using the surgical clipping method. Postoperative follow-up revealed a body temperature of 38.5 °C, tachycardia (114/min), hypotension (90/60 mmHg), and mild preibial edema. A pansystolic murmur was detected at the apex during cardiac auscultation. CTA showed no evidence of subarachnoid hemorrhage or intracranial aneurysm. Transthoracic echocardiography revealed vegetation in the mitral valve, which is indicative of infective endocarditis. Transesophageal echocardiography was planned to further evaluate the mitral valve structure. The patient was transferred to the cardiology intensive care unit. Blood cultures grew *E. faecalis*, whereas cerebrospinal fluid cultures remained negative. The patient was re-consulted for infectious diseases, and cultures were repeated according to the IE protocol. Parenteral antibiotics were initiated for *E. faecalis* endocarditis. Significant vegetation was detected on both mitral leaflets on transesophageal echocardiography, with 20 mm mobile vegetation and chordal rupture on the posterior leaflet and 14 mm vegetation on the anterior leaflet. Severe mitral regurgitation was also detected (Figure 1a). The patient was transferred to the cardiovascular surgery department for mitral valve replacement. Although biological mitral valve replacement was recommended, the patient preferred mechanical valve replacement to avoid another heart surgery in 15-20 years. An opinion was obtained from the neurosurgeon regarding the risk of intracranial bleeding associated with mechanical valve replacement, which was presented to the patient. After discussing the risks, the patient and his relatives accepted the risks and insisted on mechanical mitral valve replacement. Informed consent was obtained from the patients prior to the procedure. However, rapid clinical deterioration and acute pulmonary edema necessitated emergency cardiac surgery.

### Surgical Procedure

After adequate heparinization, median sternotomy was performed. Aortic artery cannulation and bicaval venous cannulation from the right atrium were performed. A vent cannula was inserted into the right upper pulmonary vein. Cardiac arrest was induced using antegrade del Nido cardioplegia after aortic cross-clamping. The mitral valve was accessed through a transeptal approach, revealing vegetation on the anterior and posterior leaflets, as well as ruptured chordae tendinea (Figures 1b-d). Both mitral leaflets and their associated vegetation were excised (Figures 2a, b). The ruptured chordae tendinea were also excised. The area was thoroughly irrigated with physiological saline and aspirated. Mechanical mitral valve replacement (St. Jude, no.: 33, USA) was performed (Figures 2c, d). After the procedure, the cross-clamp was removed, and weaning from CPB was uneventful (Video 1). Intraoperative transesophageal echocardiography showed that the implanted mitral valve was functioning properly with no significant transvalvular gradient. The patient was extubated early in the postoperative period. *E. faecalis* was cultured in tissue and

blood. The patient received *E. faecalis*-sensitive parenteral antibiotics for six weeks and was discharged without any complications. Clinical and echocardiographic follow-up at six months postoperatively were unremarkable.

## Discussion

*E. faecalis* is an opportunistic Gram-positive bacterium that lives in the gastrointestinal tract of humans. *E. faecalis* accounts for 5-15% of all IE cases. It is the third leading cause of IE worldwide, after *Viridans streptococci* and *Staphylococcus aureus*. *E. faecalis* IE is a serious infection with high mortality (20-40%) despite significant advances in antimicrobial therapy. Unlike other types of infective endocarditis, approximately 40% of patients with *E. faecalis* require surgical intervention[2].

The diagnosis of IE is usually based on clinical findings, blood cultures obtained following the endocarditis protocol, and echocardiographic findings.

IE complicated by severe mitral or aortic valve stenosis or regurgitation, uncontrolled intracardiac abscess, pseudoaneurysm, fistula, rapidly enlarging vegetation, vegetation ≥10 mm with recurrent embolic events, or vegetation ≥15 mm, refractory pulmonary edema, or cardiogenic shock, despite optimal medical therapy warrants consideration of cardiac surgery[3]. We performed emergency surgery because of severe mitral insufficiency and rapidly progressing pulmonary edema.

Valve replacement is preferred for patients with infected endocarditis. Defects caused by debridement should be repaired with plegitic sutures. Valve replacement should be performed after establishing a clean, solid, and safe area for valve replacement has been established[4].

Atherosclerosis, diabetes, chronic kidney disease, male sex, advanced age, and immunosuppressive states are important risk factors for mycotic aneurysms[5].

CTA, magnetic Resonance Imaging, and digital subtraction angiography (DSA) are used to diagnose intracranial mycotic aneurysms.

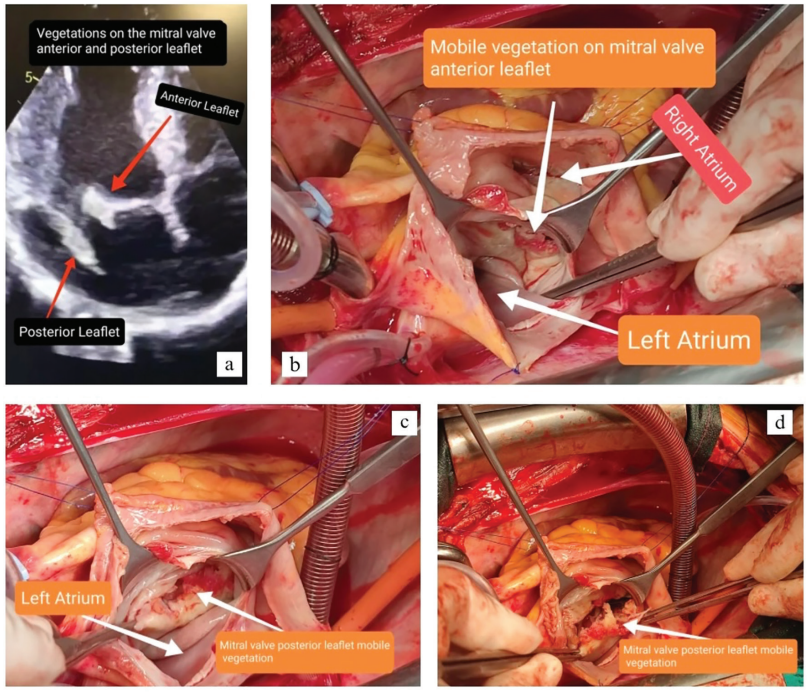


**Figure 1. a)** Echocardiographic image of vegetation on the mitral valve **b)** Surgical image of vegetation on mitral valve **c)** Surgical image of vegetation on the mitral valve posterior leaflet **d)** Surgical image of mobile vegetation on the mitral valve posterior leaflet

DSA is the gold standard for diagnosis. The shape, number, localization, and size change of the mycotic aneurysm is evaluated in periodic DSA. Treatment of intracranial mycotic aneurysms depends on the general health of the patient, characteristics of the aneurysm, and presence of rupture. If the patient is at very high surgical risk and the aneurysm has not ruptured, conservative treatment with antibiotics is recommended based on the results of blood and cerebrospinal fluid cultures. Surgical treatment of mycotic aneurysm includes open surgery and clipping of the aneurysm. In addition, with endovascular surgery, occlusion of the aneurysmal artery can be performed using coils or liquid embolice agents[1]. As in this case, patients with IE may present to the hospital with initial neurological complications. Care should be taken when interpreting the differential diagnosis.

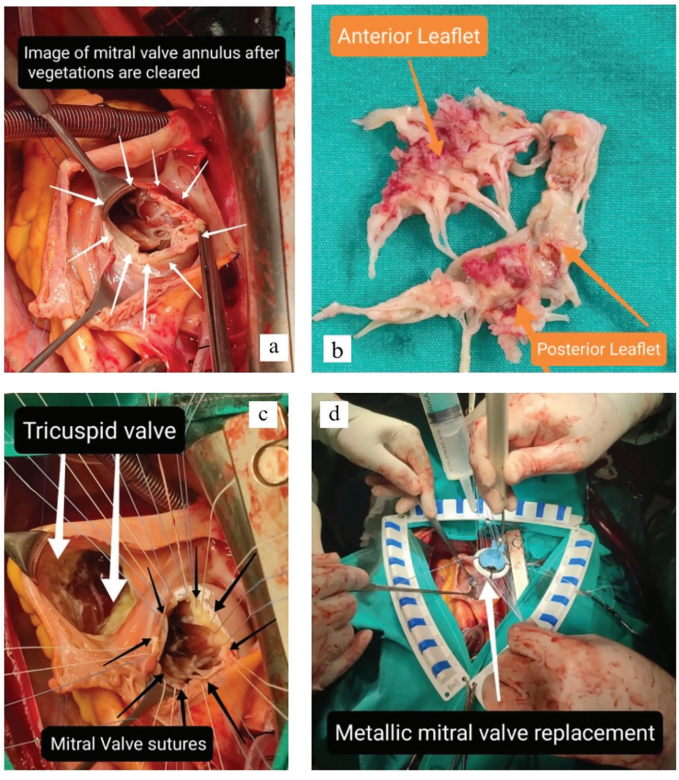


**Figure 2. a)** Image of vegetation on the mitral valve **b)** Image of an infected mitral valve **c)** Placement of mitral valve sutures **d)** Mechanical mitral valve replacement image

## Conclusion

*E. faecalis* is a Gram-positive bacterium that can cause rapidly progressive endocarditis and requires urgent and aggressive treatment, including surgical intervention. This case demonstrates the importance of early diagnosis, appropriate antibiotic therapy, early surgical intervention, and multidisciplinary management for the successful treatment of complicated infective endocarditis. In this study, we shared a case of *E. faecalis* mitral valve endocarditis accompanied by subarachnoid hemorrhage and mycotic intracranial aneurysms, which are very rarely reported in the literature. A patient with undiagnosed IE may present to the emergency department due to initial neurological complications. IE should be considered in the differential diagnosis.

### Ethics

**Informed Consent:** Informed consent was obtained from the patients prior to the procedure.

### Authorship Contributions

Surgical and Medical Practices: Kahraman N, Binicier NA, Concept: Kahraman N, Binicier NA, Design: Binicier NA, Data Collection and/or Processing: Binicier NA, Analysis and/or Interpretation: Binicier NA, Literature Search: Binicier NA, Writing: Binicier NA.

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**Video 1.** All stages from the beginning to the end of mitral valve infective endocarditis
https://www.youtube.com/watch?v=aewzibB4_rk