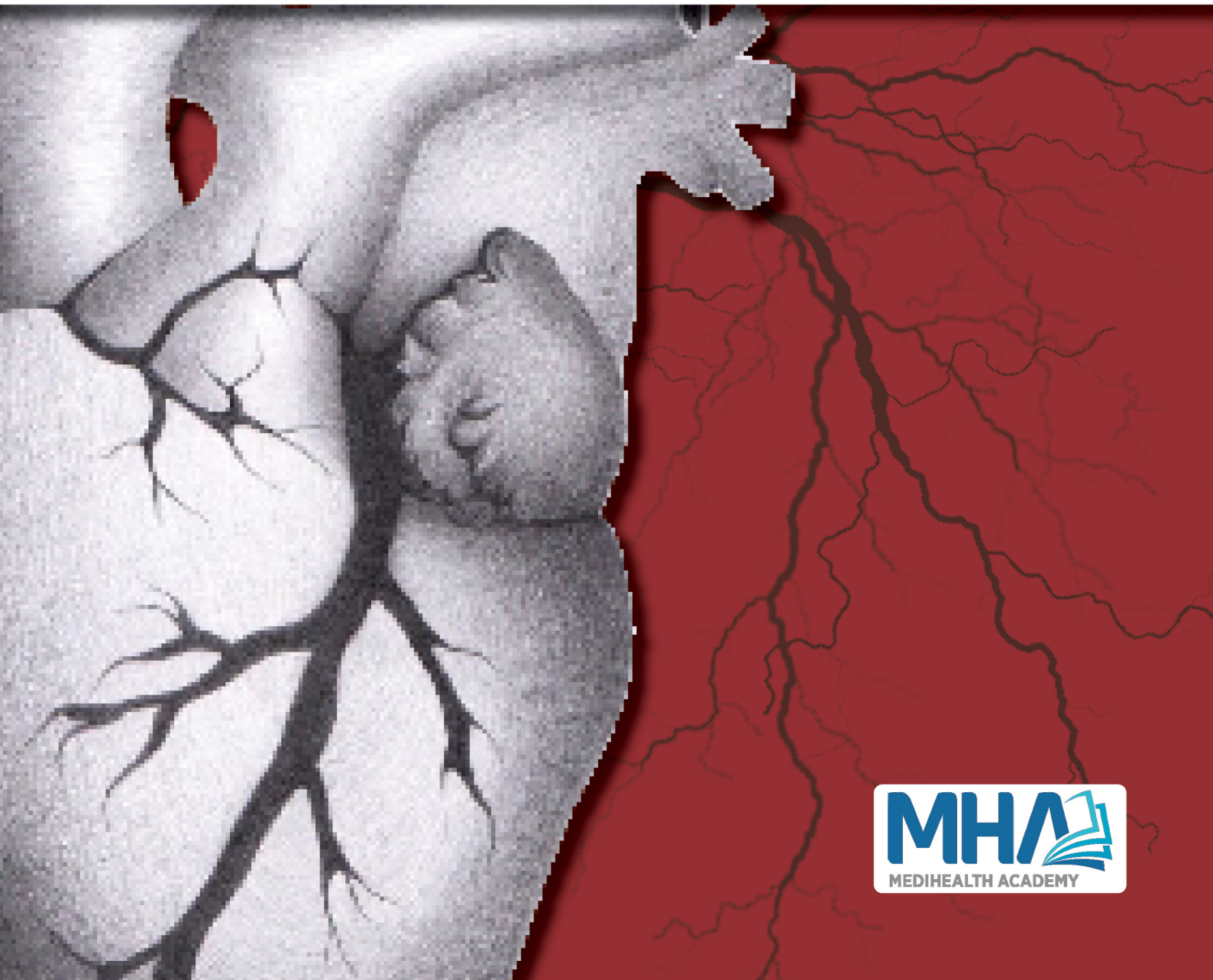
e-ISSN: 2980-1397

Journal of CARDIOLOGY & CARDIOVASCULAR SURGERY

Volume: 3 Issue: 1 Year: 2025

JCCVS



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Dear Colleagues,

I am excited to share with you the first issue of the 3rd year of the Journal of Cardiology & Cardiovascular Surgery.

In this issue, there are 4 original research articles, three related to cardiology and one related to cardiovascular surgery. First of all, you will read the original study by Arslan et al. on the interesting topic of obesity paradox and STEMI.

The second original research article is the study by Yıldırım et al. on the effect of ranolazine, which is frequently used in cardiology, on erectile dysfunction in men with coronary artery disease.

The last cardiology-related research article in this issue of our journal is the article by Tellice et al. titled "Association of echocardiographic diastolic tricuspid regurgitation with other echocardiographic parameters, survival scores and functional capacity in patients with advanced functional mitral regurgitation". In this study, they investigated the effects of DTR on right ventricular function, survival rates and functional capacity in patients with advanced FMR.

The only cardiovascular surgery related research article in this issue is the retrospective study by Doğan et al. on pediatric patients with pericardial effusion undergoing cardiovascular surgery, which is a specific field.

Finally, you will see the letter to the editor by Özbakkaloğlu A. to the case report of Beyazal et al. titled "Concomitant pulmonary thromboendarterectomy and supracoronary ascending aorta replacement: case report" in the Journal of Cardiology & Cardiovascular Surgery 2024:2;3. I am sure our readers who are cardiovascular surgeons have their own ideas on this subject.

I would like to say thank you to the authors, referees, editorial team and publisher for their efforts in this issue. We will continue to try to convey the contributions you will make to science and literature in a fast and high quality way.

Best regards,

Esra Polat, MD.

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ORIGINAL ARTICLES

LETTER TO THE EDITOR

Journal of
Cardiology & Cardiovascular
Surgery

Original Article

DOI: 10.51271/JCCVS-0047

The relationship between obesity paradox and C-reactive protein in patients with ST-segment-elevation myocardial infarctions

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Cite this article: Arslan GY, Toprak C, Karataş M, Soner S. The relationship between obesity paradox and C-reactive protein in patients with ST-segment-elevation myocardial infarctions. *J Cardiol Cardiovasc Surg.* 2025;3(1):1-4.

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Received: 28/02/2024 ◆ **Accepted**: 12/12/2024 ◆ **Published**: 27/03/2025

ABSTRACT

Aims: Inflammation plays a very important role in the pathogenesis of coronary artery disease (CAD) and its prognosis. Especially; C-reactive protein (CRP) is associated with poor prognosis in patients with CAD. In this study, the relationship between CRP levels and body-mass index (BMI) was investigated in patients who underwent primary coronary intervention (PCI) due to ST-segment elevation myocardial infarction (STEMI).

Methods: Between January 2015 and February 2016, 132 patients who underwent PCI due to acute STEMI were included in the retrospective study. Patients were classified into two groups: (group 1:BMI <25kg/m^2 n:27 and BMI >35 kg/m^2 n:9, total:36 patients; group 2: 25<BMI<30 kg/m^2 n:58 and 30<BMI<35 kg/m^2 n:38, total 96 patients). Class 2, 3 obese patients and normal weight patients constituted group 1 whereas pre-obese and class 1 obese patients were included in group 2. The patients are grouped in this way because the prognosis of the first group is worse in obesity paradox studies.

Results: CRP was found to be significantly lower in STEMI patients with 25>BMI<35. Whereas it was significantly higher in STEMI patients with 25<BMI>35.

Conclusion: In this study, the relationship between CRP levels and BMI was investigated in patients who underwent PCI due to STEMI. The reasons for the better prognosis of mildly overweight and class 1 obese patients with STEMI diagnosis may be the low values of CRP which has many effects on atherosclerotic plaque formation.

Keywords: ST-segment elevation myocardial infarction, C-reactive protein, obesity paradox

INTRODUCTION

The prevalence of obesity has increased significantly worldwide, becoming a major health and social problem.[1] Obesity is associated with increased risks of hypertension, metabolic syndrome, and type 2 diabetes mellitus, all strong risk factors for coronary artery disease (CAD).[2,3] Despite these adverse cardiovascular effects of obesity, numerous studies have revealed better cardiovascular outcomes in obese individuals which is defined as 'obesity paradox'.[4-6] The aetiology of obesity paradox remains largely unexplained.

Weight that is higher than what is considered as a healthy weight for a given height is described as overweight or obese. Body-mass index (BMI) is used as a screening tool for overweight or obesity. According to the World Health Organization (WHO); BMI was categorized as follows: underweight (BMI<18.5 kg/m^2), normal (BMI 18.5≤24.9 kg/m^2), overweight (BMI 25≤30 kg/m^2), and obesity (BMI≥30 kg/m^2). Obesity is classified as class I for a BMI between 30 and 34.9 kg/m^2, class II for a BMI between 35 and 39.9 kg/m^2, and class III for a BMI≥40 kg/m^2.

Inflammation plays a very important role in the pathogenesis of CAD and its prognosis.[7] Especially; many clinical studies indicate that C-reactive protein (CRP) is associated with poor prognosis in patients with CAD.[8]

In this study, the relationship between CRP levels and BMI was investigated in patients who underwent primary coronary intervention (PCI) due to ST elevation myocardial infarction (STEMI).

METHODS

The study was conducted with the permission of Health Sciences University Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.12.2024, Decision No: 268). Between January 2015 and February 2016, 132 patients who underwent PCI due to acute STEMI were included in the retrospective study. The confidential information of the patients was protected according to current national normative. The study protocol

was approved by the ethics committee and Helsinki Declaration.

ACS with ST segment elevation was defined as the presence of chest pain with persistent ST-segment elevation of at least 0.1 mV in at least two contiguous leads or a new left bundle-branch block.

Major exclusion criteria included cardiogenic shock, clinically significant hepatic disease, infection, patients who were followed-up by non-PCI medical treatment, and CRP>10 mg/dl. This study evaluated demographic characteristics, risk factors and laboratory findings. Patients were classified into two groups: (group 1: BMI<25kg/m² n:27 and BMI>35 kg/m² n:9, total:36 patients; group 2: 25<BMI<30 kg/m² n:58 and 30<BMI<35 kg/m² n:38, total 96 patients). Class 2,3 obese patients and normal weight patients constituted group 1 whereas pre-obese and class 1 obese patients were included in group 2. The patients are grouped in this way because the prognosis of the first group is worse in obesity paradox studies.[4-6] The characteristics of the patients consisted of medical history (diabetes mellitus, hypertension, hyperlipidemia, previous myocardial infarction, smoking, family history), the laboratory findings (glucose, creatinine, cardiac enzymes, serum cholesterol, CRP, hemoglobin, hematocrit, leukocyte, lymphocyte, neutrophil, mean platelet volume, platelets, albumin, total protein, bilirubin and left ventricular ejection fraction (LVEF).

Statistical Analysis

Numerical variables were mean±standard deviation; categorical variables were frequency and percentage. Patients were divided into 2 groups according to BMI. The student-t test was used to compare normal distribution variables and the Mann-Whitney U test was used to compare non-normal distributions. Chi-square test was used to compare categorical variables. Patients were divided into 4 groups according to BMI and one way analysis of variance (ANOVA) was applied to compare CRP values. SPSS 16.0 (Statistical Package for Social Sciences) program was used for statistical analysis of the data in the study. p value<0.05 was considered statistically significant for all tests.

RESULTS

The demographic characteristics of 132 patients' (115 men, 17 women), risk factors, laboratory results are listed in **Table 1**. There was no difference between two groups according to history of coronary artery disesase and three vessels disease. There was no statistically significant difference between the two groups regarding demographic features, risk factors and LVEF (**Table 2**). Total cholesterol (192.50±43.99; 175.30±41.22, p=0.044), hemoglobin (13.92±1.40; 13.23±1.98, p=0.026), hematocrit (42.42±4.19; 40.51±5.61, p=0.037) and triglyceride (179.59±99.13; 140.25±53.12, p=0.026) levels were significantly higher in group 2 compared to group 1. On the other hand, CRP was significantly higher in group 1 (p=0.004) (**Table 3**). Subgroup analysis was performed to assess CRP according to the patients' BMI. Patients were divided into 4 subgroups according to BMI: subgroup 1 BMI<25 (n:27), subgroup 2 25<BMI<30 (n:58), subgroup 3 30<BMI<35 (n:38), subgroup 4 BMI>35 (n:9). The mean CRP values of the subgroups are given in **Table 4**. The distribution of CRP values according to BMI is shown in **Figure**. There was no statistically significant difference between CRP values of the subgroups. CRP was found to be significantly lower in STEMI patients with 25>BMI<35.Whereas it was significantly higher in STEMI patients with 25<BMI>35.

Table 1. Baseline demographics and medical history of the study population

	Group 1 BMI>35 and BMI<25 (n=36)	Group 2 35≥BMI>25 (n=96)	p value
Patient characteristics			
Age years	59.5±9.82	54.3±12.2	0.250
Gender, male, n	31	84	0.518
BMI (kg/m²)	26.2±6.0	28.8±2.3	0.015
Diabetes mellitus, n	13	32	0.459
Hypertension, n	14	41	0.423
Dyslipidaemia, n	12	40	0.252
Smoker (current), n	16	42	0.679
Smoker (ex), n	13	29	0.392
Chronic kidney disease, n	6	8	0.143
Previous CAD history, n	10	19	0.224
Family CAD history, n	14	50	0.124
Anterior MI, n	19	67	0.476
Three vessels, n	8	16	0.678

BMI: Body-mass index, CAD: Coronary artery disease, MI: Myocardial infarction

Table 2. Laboratory results of the study population

	Group 1 BMI>35 and BMI<25 (n=36)	Group 2 35≥BMI>25 (n=96)	p value
Laboratory data			
CRP (mg/dl)	1.88±2.14	0.75±0.81	0.004
Haemoglobin	13.23±1.98	13.92±1.40	0.026
Haematocrit	40.51±5.61	42.42±4.19	0.037
Leukocyte	12.86±3.12	12.29±3.78	0.423
Lymphocyte	1.96±0.87	1.94±0.92	0.906
Neutrophil	10.01±3.42	9.57±3.65	0.446
Mean thrombocyte volume (MPV)	8.34±0.96	8.62±1.03	0.159
Thrombocyte	238.58±47.02	234.48±52.97	0.685
Neutrophil/lymphocyte ratio	7.07±5.79	5.98±3.28	0.295
LDL	112.36±35.49	121.08±38.15	0.236
HDL	36.11±7.59	38.23±8.85	0.204
Triglyceride	140.25±53.12	179.59±99.13	0.026
Total cholesterol	175.30±41.22	192.50±43.99	0.044
Glucose	163.47±63.27	168.97±84.01	0.722
Urea (mg/dl)	38.96±22.75	33.75±10.46	0.193
Serum creatinine (mg/dl)	0.99±0.62	0.81±0.24	0.115
Initial troponin	15.28±25.97	19.21±29.51	0.482
Bilirubin	0.64±0.32	0.60±0.32	0.512
Albumin	3.69±0.44	3.78±0.38	0.217
Total protein	6.43±0.59	6.42±0.48	0.943
LVEF	49.58±11.29	49.06±10.24	0.801

BMI: Body-mass index, CRP: C-reactive protein, LDL: Low density lipoprotein, HDL: High density lipoprotein, LVEF: Left ventricular ejection fraction

Table 3. CRP values of the subgroups

	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4
CRP mg/dl	1.77±2.23	0.77±0.91	0.72±0.66	2.22±1.92

Subgroup 1: BMI<25, Subgroup 2: 25≤BMI<30, Subgroup 3: 30≤BMI<35, Subgroup 4: BMI≥35, CRP: C-reactive protein, BMI: Body-mass index

Table 4. Statistical relations of the subgroups with each other (p value)

	Supgroup 1	Supgroup 2	Supgroup 3	Supgroup 4
Supgroup 1	-	0.017	0.022	0.848
Supgroup 2	0.017	-	0.999	0.027
Supgroup 3	0.022	0.999	-	0.027
Supgroup 4	0.848	0.027	0.027	-

Subgroup 1: BMI<25, Subgroup 2: 25≤BMI<30, Subgroup 3: 30≤BMI<35, Subgroup 4: BMI≥35, BMI: Body-mass index

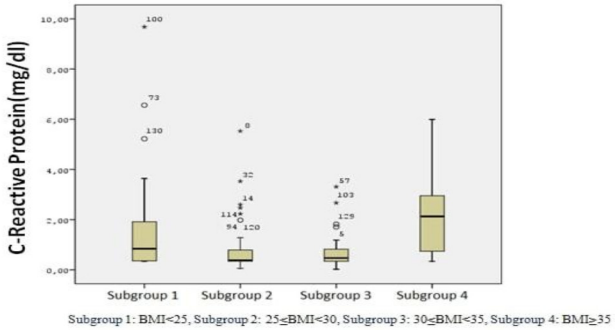

Figure. The distribution of CRP values according to BMI
CRP: C-reactive protein, BMI: Body-mass index

DISCUSSION

CAD is one of the most important causes of death in the world. Rupture of atherosclerotic plaques and plaque erosion in the coronary arteries cause acute coronary syndrome. CRP is an acute phase reactant that plays a role in atherosclerotic plaque formation and plaque rupture. The reference hs-CRP value has been found to be associated with a poor prognosis when measured >3 mg/L in stable CAD and >10 mg/L in acute coronary syndromes.[9] JUPITER and PROVE-IT clinical trials have shown that clinical outcome is better with low CRP in patients receiving statin therapy.[10,11] The relationship between inflammation and very weak and morbidly obese patients, who are reported to have poor prognosis for CAD, has been investigated in this clinical trial.

In the obesity paradox of CAD, overweight patients and type 1 obese patients have been shown to have a better prognosis than normal weight patients, type 2 and 3 obese patients.[12] When the long term results of STEMI patients over 65 age is evaluated, similar obese paradox is observed, the best prognosis is documented for moderately obese (30<BMI<35) group.[13]

CRP is an acute phase protein produced in liver cells in response to IL-6 and TNFa cytokines. It has been shown that CRP is also produced by the atherosclerotic intima layer.[14] It is highly sensitive, and may indicate nonspecific inflammation, tissue damage, and infection. Increased risk of cardiovascular disease has been detected in patients with increased inflammatory markers such as CRP, leukocyte, fibrinogen and IL-6.[15] Inflammatory cells, inflammatory proteins, and vascular cells inflammatory signals has an important role in pathogenesis of different levels of atherosclerosis including atheroma plaque accumulation, plaque instability, rupture, post angioplasty and restenosis.[16] In the buildup of stabilize plaque, it is shown that CRP is accumulated on LDL and causes macrophages to uptake more LDL and consequently causes them to transform into foam cells. There is a rich literature that shows the relationship between acute coronary syndrome and inflammation. One of the most investigated markers of inflammation in acute coronary syndromes is the CRP.[17,18] Oltrona et al.[19] discovered that CRP is an independent risk factor in AKS and a 30-day predictor of mortality. In a study with 1078 STEMI patients, CRP and WBC are recognized as independent in-hospital mortality predictors.[20] Another similar study claimed that CRP indicates the seriousness of infarct in STEMI and a predictor of complications.[21] High CRP levels is detected in thin-capsule atheroma plaque which is identified with OCT. This shows that inflammatory period takes an active role in plaque activation.[22] Correlated regression of CRP values after plaque formation stabilized by high dose statin administration at post STEMI proves that inflammation and consequently CRP are effective on motile plaque.[23] In our study, there was no statistical difference between the groups in terms of-inflammation markers except CRP. Significantly different levels of CRP among the groups may indicate that CRP-mediated inflammation may be one of the causes of obesity paradox. In the subgroup analysis, the distribution of CRP levels in groups was similar to the U-Shaped curve in previously reported obesity paradox studies.

Adiponectin secreted from adipose tissue stimulates fatty acid oxidation in skeletal muscle and inhibits glucose production in the liver, providing an improvement in whole-body energy homeostasis. Adiponectin is also a classic anti-inflammatory agent that reduces inflammation in various cell types by Adipo R1 and R2 signaling mechanisms. The anti-inflammatory, anti-hypertrophic and antiapoptotic properties of adiponectin cause vasculature, heart, lung and colon protection.[24,25] One study showed that adiponectin was inversely proportional to CAD progression and CRP was directly proportional.[26] Adiponectin levels were found to be reduced by abnormal glucose metabolism.[27] This suggests that adipose tissue can be protective by endocrine effect to a certain level. However, with the progressive deterioration of glucose metabolism in advanced stages of obesity, it may cause the complications of metabolic syndrome. Obesity complications are expected to be less frequent in overweight and type 1 obesity compared to type 2 and 3 obesity. As a result, the protective effects of adiponectin may be expected to be more prominent in overweight and type 1 obese patients. The anti-inflammatory effects of adiponectin may lead to decrease in CRP levels and suppression of CRP related tissue effects. One of the reasons for the worse survival rates of normal weight people may be the lack of cardio-protective effects of adipose tissue.

Limitations

First of all our clinical study are retrospective, single centered, and has small number of patients. Future studies may be needed.

CONCLUSION

CRP was found to be significantly lower in STEMI patients with 25>BMI<35. Whereas, it was significantly higher in STEMI patients with 25<BMI>35. One of the reasons for the better prognosis of mildly overweight and class 1 obese patients with STEMI diagnosis may be the low values of CRP which has many effects on atherosclerotic plaque formation.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Health Sciences University Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.12.2024, Decision No: 268).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of
Cardiology & Cardiovascular
Surgery

Original Article

DOI: 10.51271/JCCVS-0048

The effect of ranolazine on erectile dysfunction in coronary artery disease patients

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Cite this article: Turgay Yıldırım Ö, Aydın F, Akşit E, Hüseyinoğlu Aydın A, Dişikırık T, Özgeyik M. The effect of ranolazine on erectile dysfunction in coronary artery disease patients. *J Cardiol Cardiovasc Surg.* 2025;3(1):5-9.

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Received: 24/01/2025 ◆ **Accepted**: 17/03/2025 ◆ **Published**: 27/03/2025

ABSTRACT

Aims: Erectile dysfunction (ED) and coronary artery disease (CAD) are disorders with similar pathophysiology and the prevalence of ED may be as high as 75% in cardiovascular patients. Ranolazine is a second line therapy in CAD patients with angina. It inhibits the late sodium current in cardiomyocytes. It also has positive effects on endothelial dysfunction which is a common disruption on both CAD and ED. We aim to evaluate the effect of ranolazine on ED in CAD patients with angina complaints.

Methods: A total of 37 CAD patients were included for the study. Ranolazine was started to patients with angina symptoms. Sexual Health Inventory for men (SHIM) questionnaire was used to evaluate the status of ED. The questionnaire was applied to patients before the start and at the 6th month of ranolazine treatment.

Results: The SHIM scores of each question did not change significantly after the follow up period (p>0.05). The total SHIM score at the beginning was 10.7±5.4 and after 6 months the SHIM score was 10.7±6.3 and the difference was statistically insignificant (p=0.757). The changes in the SHIM classes were not statistically significant (p=0.454).

Conclusion: Ranolazine does not have positive or negative effects on ED at CAD patients with angina pectoris. Further studies with larger patient population must be done to confirm the results of the study.

Keywords: Coronary artery disease, erectile dysfunction, ranolazine, Sexual Health Inventory for men questionnaire

INTRODUCTION

Erectile dysfunction (ED) is defined as an inadequate penile erection or inability to sustain an erection that causes dissatisfaction during sexual intercourse.[1] Etiology behind ED may be explained by psychogenic, neurogenic, hormonal, drug-induced, vasculogenic and lifestyle factors or systemic disorders.[2] Cardiovascular diseases and ED have similar risk factors like age, diabetes mellitus, insulin resistance, hypertension, smoking, total cholesterol, low density lipoprotein cholesterol levels and high body-mass index.[3] The prevalence of ED in coronary artery disease (CAD) patients can be as high as 75%.[4,5] The pathophysiology under ED and CAD is also similar. Endothelial dysfunction, chronic inflammation and the artery size hypothesis are used to explain the mechanism underneath.[6,7] Many drugs are used for the treatment of CAD patients which also have effects on ED. Thiazide diuretics and most beta blockers have negative effects while vasodilator beta blockers, calcium antagonists have neutral impact and nebivolol has positive impact on ED. Adjusting the treatment of the patients may improve the problem because cardiac patients already have a tendency for ED and many drugs worsen the underlying situation.[8-10]

Ranolazine is a second line antianginal therapy for CAD patients.[10] Ranolazine selectively inhibits the late sodium current in cardiomyocytes. It reduces intracellular calcium overload and increase the oxygen consumption.[11] Ranolazine also has anti-inflammatory and antioxidant effects which may be important for microvascular angina.[12] ED was thought to be a psychogenic disorder since late 20th century but now it is recognized as a physiologic disorder affecting the penile circulation.[13,14] The artery size hypothesis states that atherosclerosis affects all major vascular beds but smaller vascular beds like penile artery will be affected earlier compared to coronary artery which are larger in diameter and will tolerate atherosclerosis at an extent. But all major arteries will be effected to the same extend in the end.[5,7] The effects of ranolazine on endothelium and vascular bed may improve the disruptions on penile tissue since both ED and CAD has similar mechanism and ranolazine effects the tissues by several ways and improves endothelial function and electrolyte disruptions.[15,16]

While ranolazine's primary mechanism of action involves the inhibition of the late sodium current in cardiomyocytes,

leading to reduced intracellular calcium overload and improved myocardial relaxation[11], its potential effects on penile function remain unclear. Unlike cardiac tissue, the penile nerve conduction system and vascular regulation rely on a complex neurovascular coupling mechanism, with nitric oxide (NO) playing a central role in smooth muscle relaxation and penile erection.[13,14] Ranolazine has been shown to enhance endothelial nitric oxide synthase (eNOS) activity and reduce oxidative stress in peripheral vascular beds, which could theoretically improve penile blood flow and smooth muscle relaxation.[15,16] However, the physiological differences between cardiac and penile tissues, particularly in terms of nerve conduction and vascular demands, may limit the direct applicability of ranolazine's effects. This study aims to explore whether ranolazine's systemic vascular and endothelial benefits can translate into improvements in erectile function in CAD patients.

METHODS

The study was conducted with the permission of Eskişehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (Date: 18.09.2018, Decision No: 12) and patients provided written informed consent. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The patient population was selected from 200 male patients with angina complaints who were admitted to the cardiology outpatient clinic between 15.11.2018 and 30.04.2019. These patients had CAD proven by coronary angiography and extended-release ranolazine treatment was needed to be started for angina pectoris. Patients under 18 years old, patients without sexual partners, patients who use phosphodiesterase inhibitors, patients whom the ranolazine use in not recommended were not included. After excluding those patients who did not agree to participate in the study, did not show up for their follow-up examination, and had irreversible ED due to urological reasons (eg. trauma), the remaining 37 people were included in the study.

The Sexual Health Inventory for men (SHIM) questionnaire was used for the evaluation of ED. The questionnaire consists of five questions. The scores changes between 1 to 25. According to the scores of the questionnaire, ED was classified into 5 categories. The scores between 1-7 represents "severe ED", 8-11 represents moderate ED, 12-16 represents mild to moderate ED, 17-21 represents mild ED and 22-25 represents no ED.[17] This questionnaire was administered to CAD patients before the ranolazine treatment and 6 months after the beginning of ranolazine treatment. The questions and appointed scores are shown in **Table 1**.

This study was designed prospectively. Ranolazine 500 mg twice a day was started in all patients participating in the study. SHIM questionaire was applied before treatment was initiated. After 6 months of follow-up, SHIM questionnaire was applied to patients who still continued to use ranolazine 500 mg twice a day.

Statistical Analysis

Data are presented as mean±standard deviation (SD) and as proportions for categorical variables. Distribution of the data for normality was tested by the Shapiro–Wilk test and homogeneity of group variances were tested by the Levene test. SHIM scores and comparison between SHIM categories are evaluated by Wilcoxon signed rank test. $p<0.05$ was considered to be statistically significant. The data were analyzed using SPSS 20.0 (IBM SPSS Ver. 20.0, IBM Corp, Armonk NY, USA).

Table 1. The Sexual Health Inventory for Men (SHIM) questionnaire

How do you rate your confidence that you could get and keep an erection?	Very low: 1 Low: 2 Moderate: 3 High: 4 Very high: 5
When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No sexual activity: 0 Almost never or never: 1 A few times (much less than half the time): 2 Sometimes (about half the time): 3 Most times (much more than half the time): 4 Almost always or always: 5
During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did not attempt intercourse: 0 Almost never or never: 1 A few times (much less than half the time): 2 Sometimes (about half the time): 3 Most times (much more than half the time): 4 Almost always or always: 5
During sexual intercourse, how difficult was it to maintain your erection until completion of intercourse?	Did not attempt intercourse: 0 Extremely difficult: 1 Very difficult: 2 Difficult: 3 Slightly difficult: 4 Not difficult: 5
When you attempted sexual intercourse, how often was it satisfactory for you?	Did not attempt intercourse: 0 Almost never or never: 1 A few times (much less than half the time): 2 Sometimes (about half the time): 3 Most times (much more than half the time): 4 Almost always or always: 5

RESULTS

A total of 37 CAD patients were included in the study. Mean age of study population was 60.6±8.9. 70.3% of the patients (n=26) had hypertension and 35.1% had diabetes mellitus. The ejection fraction value was 58.6±5.9 and mean NYHA class of the patients were 1.3±0.5. Atrial fibrillation patients constituted 8.1% (n=3) of the sample and mean heart rate of these patients was 77.5±3.5 bpm. Remaining 91.9% of the patients had sinus rhythm with a mean heart rate of 69.5±7.5 bpm. The medications of the patients were given at **Table 2**.

At the beginning of the study; 35.3% (n=12) of the patients had severe ED, 2.9% (n=1) had moderate ED, 47.1% (n=16) had mild to moderate ED and 14.7% (n=5) had mild ED. After 6 months use of ranolazine; 35.3% (n=12) of the patients had severe ED, 17.6% (n=6) had moderate ED, 29.4% (n=10) had mild to moderate ED, 11.8% (n=4) had mild ED and 5.9% (n=2) of the patients had no ED. The changes in the SHIM classification groups were not statistically significant (p=0.454). 8.1% (n=3) of ED patients' SHIM classes were progressed and 16.2% (n=6) of the patients classes were regressed after 6 months of treatment. The remaining 75.7% of the sample remained in the same class.

The SHIM scores of each question did not change significantly after the follow up period (p>0.05). The total SHIM score at the beginning was 10.7±5.4 (**Figure 1**) and after 6 months the SHIM score was 10.7±6.3 (**Figure 2**). The change was not statistically significant (p=757). The changes in the scores

Table 2. Baseline characteristics of the study population

Age, years	60.6±8.9
Hypertension	26 (70.3%)
Diabetes mellitus	13 (35.1%)
Electrocardiography	34 (91.9%) sinus rhythm 3 (8.1%) atrial fibrillation
Ejection fraction	58.6±5.9
New York Heart Association classification	1.3±0.5
Ranolazine dose	473.0±52.2
Beta blockers	27 (73.0%)
Calcium channel blockers	4 (10.8%)
ACEIs	16 (43.2%)
ARBs	8 (21.6%)
Spironolactone	4 (10.8%)
Thiazide diuretics	10 (27.0%)
Other diuretics (Indapamide, furosemide)	15 (40.5%)
Digoxin	1 (2.7%)
ASA	23 (62.2%)
Anticoagulant	3 (8.1%)
P2Y12 inhibitors	6 (16.2%)
Statin	23 (62.2%)

Data are expressed as mean±standart deviation or number (%), ACEIs: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, ASA: Acetylsalicylic acid

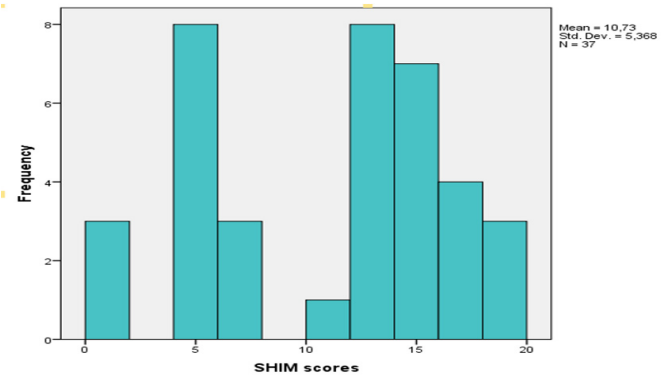

Figure 1. The total SHIM score of the patients at the beginning of the ranolazine treatment
SHIM: The Sexual Inventory for men

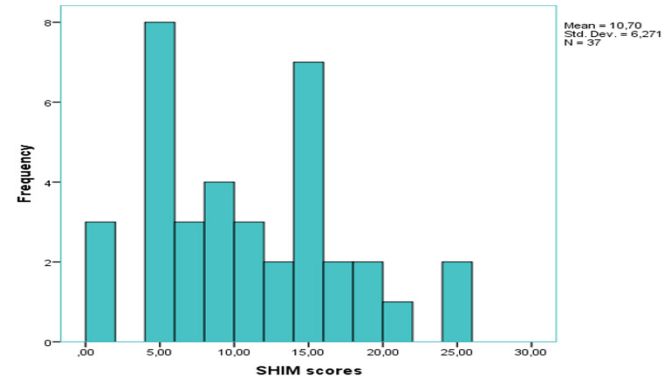

Figure 2. The total SHIM score of the patients at the 6th month of the ranolazine treatment
SHIM: The Sexual Inventory for men

were given at **Table 3**. The individual changes of patients at the SHIM score are given in **Figure 3**.

DISCUSSION

We studied the effect of ranolazine by using SHIM score at the beginning and at the sixth month of treatment. Our study revealed that ranolazine has no statistically significant positive or negative effect on ED at CAD patients.

Table 3. Changes at SHIM score results after ranolazine use

	Before use	6th month	p
Question 1	2.2 ± 0,9	2.2±1.1	0.873
Question 2	2.0±1.1	2.0±1.3	0.967
Question 3	2.1±1.2	2.1±1.3	0.874
Question 4	2.2±1.4	2.2±1.2	0.791
Question 5	2.2±1.2	2.2±1.4	0.608
Total SHIM score	10.7±5.4	10.7±6.3	0.757
ED classification*	2.3±1.1	2.3±1.2	0.454

*The classification according to the SHIM scores. The scores of 1-7 represents severe ED (group 1), 8-11 represents moderate ED (group 2), 12-16 represents mild to moderate ED (group 3), 17-21 represents mid ED (group 4) and 22-25 represents no ED (group 5). ED: Erectile dysfunction, SHIM: The Sexual Inventory for men

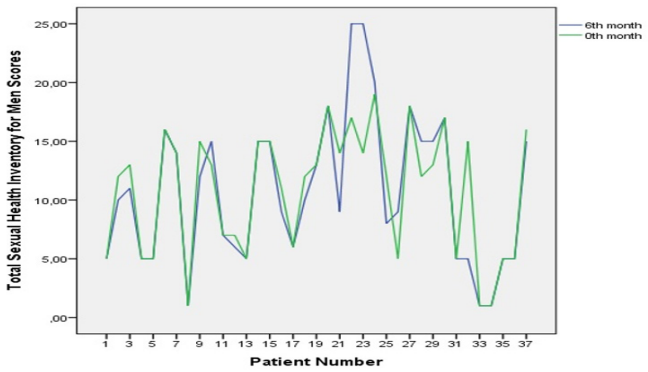

Figure 3. Individual changes in the SHIM scores after ranolazine treatment
SHIM: The Sexual Inventory for men

CAD and ED coexist in patients due to similar pathophysiological mechanisms. Patients with cardiac diseases have a probability of 39% to have ED.[18] One of the major mechanisms under these disorders is endothelial dysfunction.[19] Endothelial dysfunction affects the arteriolar system and disturbs relaxation and prevents vasodilatation in ED patients.[20] Diabetes mellitus, hypercholesterolemia also affects endothelium and both disorders lies as a risk factor on both ED and CAD. These disorders cause smooth muscle cell degradation and disrupt vasodilatation and causes ED.[20,21] Preservation of endothelial dysfunction can restore normal function in patients with atherosclerosis. Baumhakel et al.[22] showed that ivabradin has a positive effect on endothelial function at corpora cavernosa in mice on high fat diet. High fat diet was used to disrupt the normal endothelial function and ivabradin improved the penile endothelial function after 3 months of treatment. Ivabradin reduced penile fibrosis and oxidative stress and by doing so improvement at endothelial function occurred. Ranolazine also has positive effect on endothelial dysfunction.[23] Deshmukh et al.[21] showed that ranolazine improves endothelial dependent vasodilatation and improves endothelial function within 6 weeks at patents with CAD. The previous studies suggested that ranolazine which also have positive effects on endothelial function may regulate disrupted endothelial function at penile endothelium and improve ED. Penile erection is a complex process involving hormonal, psychological, and neurovascular mechanisms. NO plays a central role in this process by activating guanylate cyclase, increasing cyclic GMP levels, and reducing intracellular calcium concentrations, which ultimately relaxes smooth muscle cells in the penile vasculature.[13,14] Ranolazine has been shown to enhance eNOS activity and reduce oxidative stress in peripheral vascular beds.[15,16] These effects suggest that ranolazine could theoretically improve endothelial function and penile

blood flow, which are critical for erectile function. However, the penile vasculature and nerve conduction system differ significantly from the cardiac conduction system. Unlike cardiac tissue, penile tissue relies heavily on neurovascular coupling, where the interaction between cavernous nerves and endothelial cells is essential for smooth muscle relaxation and blood flow regulation. Ranolazine's effects on sodium and calcium channels may not directly influence these processes, which could explain the lack of significant improvement in ED observed in our study.[21-24] Although 90% of the patients who participated in our study had increased effort capacity and the angina complaints were regressed, we failed to prove that ranolazine has positive effect on ED in atherosclerotic patients.

Penile erection is regulated by hormonal and psychological events.[24] With the effect of sexual stimulation, neurotransmitters and relaxing factors are released from cavernous nerve terminals and endothelial cells of the penis. This events cause smooth muscle relaxation at the penile arterioles and arteries and blood flow increases causing penile erection. Endothelial cells and neural tissue secrete NO and by this event muscle relaxation occurs.[25] Ranolazine also increases NO production and decrease NO degradation by inhibiting receptors on endothelial cells by mediating late sodium channel current.[26,27] The positive effect of ranolazine on NO concentration may have a positive effect on ED. Because NO increases intracellular concentration of cyclic GMP which eventually decreases calcium concentrations and relaxes smooth muscle of corpus cavernosum.[25] Even though the mechanisms suggested otherwise we observed no positive effects of ranolazine on ED. There are many causes under ED like psychogenic, neurogenic, hormonal, drug-induced, vasculogenic and lifestyle factors or systemic disorders.[2] Even though there were no changes in cardiac medication, the patients may fail to inform us about other medications they use during the 6 months period of ranolazine treatment.

Limitations

There are many limitations in our study. First of all we did not evaluate psychogenic factors that may cause ED in our study. We also evaluate the status of ED by using SHIM questionnaire. The patients may answer subjectively to the questions because patients may be sensitive to the topic compared to other disorders. The results may be more objective if we used penile Doppler ultrasound instead. Also the number of patients was low which was a major limitation of the study.

CONCLUSION

We evaluated the effect of ranolazine on ED by using SHIM scoring at patient with CAD. We found out that ranolazine may not have positive or negative effects on patients with ED.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Eskişehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (Date: 18.09.2018, Decision No: 12).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of
Cardiology & Cardiovascular
Surgery

Original Article

DOI: 10.51271/JCCVS-0049

Association of echocardiographic diastolic tricuspid regurgitation with other echocardiographic parameters, survival scores and functional capacity in patients with advanced functional mitral regurgitation

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Cite this article: Tellice M, Fidan S, Avcı A, Esen AM. Association of echocardiographic diastolic tricuspid regurgitation with other echocardiographic parameters, survival scores and functional capacity in patients with advanced functional mitral regurgitation. *J Cardiol Cardiovasc Surg.* 2025;3(1):10-13.

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Received: 11/01/2025 ◆ **Accepted**: 17/03/2025 ◆ **Published**: 27/03/2025

ABSTRACT

Aims: Functional mitral regurgitation (FMR) is an important condition associated with advanced heart failure and poor prognosis. The aim of this study was to investigate the effects of diastolic (presystolic) tricuspid regurgitation (DTR) on right ventricular function, survival rates and functional capacity in patients with advanced FMR. The relationship between DTR and right ventricular systolic function and the predictive factors involved in its development were also evaluated.

Methods: The study included 64 patients with advanced FMR who were evaluated for mitraclip therapy between June 2014 and February 2015. Demographic characteristics, cardiovascular risk factors, New York Heart Association (NYHA) functional classification and laboratory data were recorded. Left and right ventricular parameters were examined by echocardiography, and the diagnosis of DTR was made by color Doppler method. Estimated survival rates were evaluated using the Seattle Heart Failure Model Score (SHFSM) with 1- and 5-year projections.

Results: DTR was detected in 14 (22%) of the patients included in the study. The majority (85.7%) of the patients in the group with DTR were in NYHA III-IV stage and had low functional capacity. DTR showed significant assocation with right ventricular fractional area change (RV FAC), right ventricular peak systolic myocardial velocity (RV Sm), TAPSE, tricuspid regurgitation, ejection fraction, pulmonary artery systolic pressure, and pulmonary vascular resistance ($p<0.05$). In addition, DTR group had lower estimated survival rates compared to SHFSM (1-year estimated survival 64%, 5-year estimated survival 35%; $p<0.001$). In Binary Logistic Regression Analysis, RV FAC and RV Sm values were found to be independent predictors for the development of DTR.

Conclusion: DTR is an important echocardiographic parameter that indicates poor prognosis in patients with advanced FMR. This study demonstrated that DTR is associated with right ventricular dysfunction and decreased estimated survival rates. Early diagnosis of DTR may provide an important contribution to clinical management and prognostic evaluation in this patient group.

Keywords: Functional mitral regurgitation, diastolic tricuspid regurgitation, survival rate, functional capacity

INTRODUCTION

Functional mitral regurgitation (FMR) is a pathology observed in structurally normal mitral valves that develops due to left ventricular (LV) remodeling in patients with ischemic and non-ischemic dilated cardiomyopathy (DCMP). FMR, occurring in 55-75% of patients with DCMP, is associated with hemodynamic deterioration and increased mortality.[1-3] Mechanisms such as LV dilatation and papillary muscle dysfunction lead to incomplete closure of the mitral valves, causing blood to backflow from the LV into the left atrium during systole.[3]

Diastolic (presystolic) tricuspid regurgitation (DTR) is an echocardiographic finding that occurs when the pressure difference between the right atrium and right ventricle (RV) reverses at the end of diastole.[4] It is usually associated with conditions such as advanced heart failure, aortic valve pathologies and atrioventricular conduction blocks.[5-7] There are limited number of studies in the literature on the pathophysiopathology of DTR and its relationship with right ventricular function in patients with congestive heart failure (CHF). Although it is known that RV dysfunction is

associated with poor prognosis, the effects of RV dysfunction on survival have not been sufficiently elucidated.[8]

This study aims to investigate the effects of DTR on right ventricular function, survival scores and functional capacity in patients with advanced FMR. In addition, we aimed to evaluate the predictive factors involved in the development of DTR and its relationship with RV systolic function. Determining the effects of DTR on prognosis may provide important information to improve clinical management and evaluation processes in this patient group.

METHODS

This study was produced from the specialisation thesis titled 'the relationship of echocardiographic diastolic tricuspid regurgitation with other echocardiographic parameters, survival scores and functional capacity in patients with advanced functional mitral regurgitation' written in Kartal in 2015. Institutional approval was obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study included 64 patients with advanced FMR who were evaluated for mitraclip therapy at İstanbul Koşuyolu Yüksek İhtisas Training and Research Hospital between June 2014 and February 2015. Demographic data (age, gender, height, weight), cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, smoking), past medical history and medications were recorded. The functional status of the patients was determined according to the New York Heart Association (NYHA) classification. FMR was found in all patients included in the study and patients with degenerative mitral valve pathology were excluded. In addition, patients with one or more of the following criteria were excluded:

- Patients with acute coronary syndrome in the last 3 months,
- Those with congenital heart disease,
- Hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia or infiltrative cardiomyopathy,
- Patients with an ICD, CRT or pacemaker device,
- Those with a mechanical prosthetic valve in the mitral or tricuspid position,
- Isolated right heart failure due to primary pulmonary hypertension,
- Those with any degree of atrioventricular block,
- Those with severe pulmonary insufficiency.

Echocardiographic Evaluation

All echocardiographic examinations were performed with the Vivid 7 Pro (GE Vingmed Ultrasound AS, Horten, Norway) in the left lateral decubitus position and during superficial respiration. Left and right ventricular parameters were measured in accordance with the American Society of Echocardiography (ASE) guidelines.[9] DTR was defined as a low velocity jet into the right atrium at the end of diastole using color Doppler.

Laboratory Investigations

Complete blood count, biochemistry panel, liver and renal function tests were evaluated on the same day. In addition, arrhythmia, signs of myocardial infarction and atrioventricular conduction disturbances were investigated by 12-lead electrocardiography (ECG).

Statistical Analysis

All statistical analyses of the data was performed with SPSS 15.0 (Statistical Package for Social Sciences) software. Continuous variables were expressed as mean±standard deviation and categorical variables as percentages. Student's t-test and Mann-Whitney U test were used for intergroup comparisons. Pearson and Spearman methods were preferred for correlation analysis. Independent predictors were determined by multivariate logistic regression analysis. The $p<0.05$ criterion was used for statistical significance.

RESULTS

The mean age of the 64 patients included in the study was 58.20±14.06 years, 50% had ischemic and 50% had DCMP. 53.1% of the participants were in NYHA III-IV stage and 46.9% were in NYHA I-II stage. Hypertension (54.7%), smoking (53.1%) and diabetes mellitus (34.4%) were the most common cardiovascular risk factors, while demographic parameters such as gender and body mass index were not significantly different between the groups (**Table 1**). DTR was detected in 22% (n=14) of the patients included in the study. Patients with DTR were generally in more advanced NYHA stages and a clinically worse functional capacity was observed in these patients.

Table 1. Demographic data and clinical characteristics of the patients

Parameter	Total (n=64)	DTR (n=14)	Non DTR (n=50)	p
Age (year)	58.20±14.06	56.5±16	58.6±13.6	0.62
Body-mass index (kg/m²)	26.61±4.57	26.3±5.5	26.7±4.3	0.76
Gender (male) (%)	%65.6	%71.4	%62.0	0.53
Hypertension (n,%)	35 (54.7)	7 (50)	28 (56)	0.76
Diabetes (n, %)	22 (34.4)	6 (42)	16 (47)	0.53
Smoking (n,%)	34 (53.1)	10 (71)	24 (48)	0.13
NYHA class (n,%)				
- NYHA I-II	30 (46.9)	2 (14)	28 (56)	<0.001
- NYHA III-IV	34 (53.1)	12 (86)	22 (44)	<0.001
CMP (ischemic)	32 (50)	7 (50)	25 (50)	1

DTR: Diastolic (presystolic) tricuspid regurgitation, NYHA: New York Heart Association, CMP: Cardiomyopathy

On echocardiographic examination, the presence of RV DTR resulted in significant deterioration in RV function parameters. In patients with DTR, the mean RV ejection fraction (EF) was around 22%, TAPSE 1.24 mm, RV Sm 8.6 cm/sec and FAC 21%. In patients without DTR, these parameters were 27.8%, 1.59 mm, 11 cm/sec and 32%,

respectively. Tricuspid regurfitation was also higher in DTR group as expected. In addition, pulmonary parameters such as PAPs and PVR were significantly higher in patients with DTR. There was no difference between groups regarding RV diameters, left atrium diameter, LV deceleration time, and left atrial volume index (**Table 2**).

Table 2. Echocardiographic parameters and univariate analysis results

	Non-DTR (n=50)	DTR (n=14)	p
LVEF (%)	27.80±7.08	22.14±6.41	0.009
EDD (mm)	6.64±0.83	6.64±0.74	0.99
ESD (mm)	5.54±0.90	5.57±0.73	0.90
LAd (mm)	4.82±0.57	5.02±0.64	0.268
LV DT (msn)	151.30±51.70	123.71±37.70	0.068
LAVi	36.89±11.14	40.15±9.13	0.320
TAPSE (mm)	1.59±0.51	1.24±0.35	0.020
RV Sm	11.04±2.72	8.67±1.56	0.003
RV FAC (%)	32.42±9.31	21.28±5.48	0.001
TR	2.12±0.92	3.07±0.73	0.001
PAPs (mmHg)	39.87±16.08	57.50±11.88	0.000
PVR (wood)	3.06±1.33	4.94±2.11	0.000

DTR: Diastolic (presystolic) tricuspid regurgitation, EDD: End-diastolic diameter, ESD: End-systolic diameter, LAd: Left atrium diameter, LAVi: Left atrial volume index, LV DT: Left ventricular deceleration time, LVEF: Left ventricular ejection fraction, RV Sm: Right ventricular peak systolic myocardial velocity, PAPs: Pulmonart artery systolic pressure, PVR: Pulmonary vascular resistance, RV FAC: Right venticular fractional area change, TR: Tricuspid regurgitation, TAPSE: Tricuspid annular plane systolic excursion

In binary logistic regression analysis, RV FAC and RV Sm values were found to be independent predictors for the development of DTR (**Table 3**). In addition, PVR and PAPs were also found to be independent predictors of DTR.

Table 3. Binary logistic regression analysis of independent echocardiographic markers of DTR

Variables	B	S.E.	Wald	Df	Sig.	Exp (B)
EF (%)	-0.107	0.101	1.125	1	0.289	0.898
RV Sm	-0.957	0.461	4.307	1	0.038	0.384
TAPSE (mm)	4.441	2.546	3.041	1	0.081	84.828
FAC (%)	-0.213	0.088	5.904	1	0.015	0.808
TR	2.302	-	-	3	0.508	-
PABs (mmHg)	0.096	0.056	2.944	1	0.086	1.101
PVR (wood)	0.594	0.404	2.163	1	0.141	1.811

DTR: Diastolic (presystolic) tricuspid regurgitation, EF: Ejection fraction, PAPs: Pulmonart artery systolic pressure, PVR: Pulmonary vascular resistance, RV Sm: Right ventricular peak systolic myocardial velocity, TAPSE: Tricuspid annular plane systolic excursion, TR: Tircuspid regurgitation

Patients with DTR show a significant decrease in 1-year and 5-year survival rates. While the 1-year and 5-year survival rates were 64% and 35%, respectively, in patients with DTR, these rates were 85% and 60%, respectively, in patients without DTR (**Table 4**).

Table 4. Survival rates and survival scores

Parameter	DTR (n=14)	Non DTR (n=50)	p
1-year survival (%)	64.0%	85.0%	<0.001
5-year survival (%)	35.0%	60.0%	<0.001

DTR: Diastolic (presystolic) tricuspid regurgitation

DISCUSSION

The aim of this study was to evaluate the effects of DTR on RV function, survival rates and clinical prognosis in patients with advanced FMR. The most important finding of our study showed that DTR had a significant negative impact on RV function, which significantly decreased the survival rates of patients. In particular, parameters such as RV EF, TAPSE, RV Sm and FAC were significantly reduced in the presence of DTR. These findings suggest that impaired RV function is a key factor in the development and progression of DTR. The presence of DTR was also found to be an important indicator associated with poor prognosis in survival prediction models such as the SHFSM.

DTR causes significant adverse effects on RV function, which may adversely affect the prognosis of patients. In our study, RV EF, TAPSE, RV Sm and FAC values were significantly lower in patients with DTR. The decrease in these parameters suggests that impaired RV function is a key factor in the development and progression of DTR. Szymanski et al.[10] associated the development of DTR with severe pulmonary hypertension and RV dysfunction, emphasizing that these parameters are important factors in the pathophysiology of DTR.

Given this evidence, DTR may have clinically important consequences in patients with advanced FMR. In our study, the presence of DTR had significant adverse effects on the survival rates of patients. Patients with DTR had significantly lower 1-and 5-year survival rates compared with patients without DTR.

There are many studies supporting our findings. According to a meta-analysis by Truong et al.[11] impaired RV function had a significant effect on the prediction of all-cause mortality in patients with FMR. According to a study by Doldi et al.[12] the presence of RV dysfunction in patients with primary mitral regurgitation was associated with a lower rate of symptomatic improvement and a higher 2-year mortality rate after mitra clip therapy. In addition, many studies have shown that RV function has a prognostic effect in pulmonary hypertension, congenital heart disease, pulmonary embolism, heart failure, cardiomyopathies, and valvular heart disease.[13-18]

An important feature of our study is that we comprehensively examined the effects of DTR on RV function in patients with advanced FMR. Compared to previous studies, this study provides a more detailed picture of the effects of DTR on patients by using multiple echocardiographic parameters to assess RV function. Furthermore, the use of survival prediction models such as the SHFSM to analyze the effects of DTR on survival rates and prognosis gave our study a deeper clinical meaning. The identification of parameters such as RV function and pulmonary pressure as independent predictors of DTR in multivariate analysis is one of the methodological strengths of our study and contributes to the prognostic value of DTR.

Limitations

Our study also has many limitations. The first one is that it is a single-center study, which may limit the generalizability of the findings. Furthermore, the relatively small number of patients makes validation difficult, especially in larger and heterogeneous groups. Our study examined RV function using echocardiographic parameters only and did not include further invasive testing or long-term follow-up data. This prevented us from assessing patients' response to treatment and the long-term effects of DTR. Furthermore, larger and longer-term studies examining the clinical management of DTR and its effects on treatment response are needed.

CONCLUSION

As a result, this study shows that DTR in patients with advanced FMR is associated with their RV function, pulmonary pressure and survival rates. Early recognition of DTR is critical for treatment and clinical monitoring in this patient group. RV dysfunction and pulmonary hypertension have been found to play an important role in the development of DTR and may adversely affect the prognosis of patients. These findings suggest that the effects of DTR on prognosis should be investigated in more detail in larger and long-term studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was produced from the specialisation thesis titled 'the relationship of echocardiographic diastolic tricuspid regurgitation with other echocardiographic parameters, survival scores and functional capacity in patients with advanced functional mitral regurgitation' written in Kartal in 2015.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of
Cardiology & Cardiovascular
Surgery

Original Article

DOI: 10.51271/JCCVS-0050

Outcomes of the pediatric patients undergoing pericardiocentesis for cardiac surgery-related massive pericardial effusion

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Cite this article: Doğan V, Donbaloğlu F, Sayıcı İU, Koç M. Outcomes of the pediatric patients undergoing pericardiocentesis for cardiac surgery-related massive pericardial effusion. *J Cardiol Cardiovasc Surg.* 2025;3(1):14-18.

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Received: 04/01/2025 ◆ **Accepted**: 22/03/2025 ◆ **Published**: 27/03/2025

ABSTRACT

Aims: In this study, we aimed to evaluate the demographic and clinical characteristics of the patients who have moderate or severe cardiac surgery related pericardial effusion and relieved by pericardiocentesis.

Methods: Twenty-one children (0-18 years of age) were identified retrospectively in a 10-year period (2010-2020) and we reviewed our medical records for demographic and clinical characteristics, management strategies and outcome of the patients.

Results: Male to female ratio was 1.1, and mean age and body weight of the patients were 79.7±56.6 months and 19.5±14 kg respectively. Of the patients (33%) had at least one complaint, most common being dyspnea (19%) and fatigue (8.5%). The mean period between heart surgery and pericardiocentesis was 30.1±13.4 days. The distribution of surgical indications was as follows; atrial septal defect (42.8%), ventricular septal defect (23.8%), endocardial cushion defect (9.5%). The mean largest diameter of effusion and amount of fluid drained were 34.9±13.4 mm and 349.3±276.1 ml respectively. Macroscopic appearance of the fluid was serous in 28.5%, hemorrhagic in 66.7% and chylous in 4.8% patient. Of the 21 patients 13 were treated with anti-inflammatory drugs; NSAID (14.8%), NSAID and colchicine (33.3%) NSAID, colchicine and corticosteroid (14.8%). On the follow up 2 (9.5%) patient died because of sepsis and heart failure. There were no procedure related complication, chronic effusion or constriction on the follow up.

Conclusion: In conclusion, post-pericardiotomy syndrome can lead to serious consequences. Therefore, patients at risk should be identified in the post-operative period and a patient-specific follow-up plan should be made. In the presence of tamponade or massive effusion, pericardiocentesis is a safe, effective and life-saving procedure in patients unresponsive to medical treatment.

Keywords: Cardiac surgery, pericardial effusion, pericardiocentesis, post-pericardiotomy syndrome

INTRODUCTION

Pericardial effusion (PE) is a common complication after cardiac surgery and is mostly due to surgical bleeding and perioperative trauma in the first week after intervention. Post-pericardiotomy syndrome (PPS) after cardiac surgery is an inflammatory process due to opening of the pericardium, pleural or both, can occur a few days to several weeks after surgery.[1,2] PPS was first described in the 1950s after rheumatic mitral stenosis surgery.[3] In studies, the frequency of PPS and PE after surgery has been reported as 3-43%, and the frequency of cardiac tamponade is 1-2%.[4-6] The median duration of the syndrome is generally 2–3 weeks with possible relapses occuring in several months after initial onset. Although the exact pathogenesis of PPS is not known, it is accepted that PPS develops as a result of an immune-related inflammatory process. Pleuropericardial injury is thought to trigger both local and systemic inflammatory/immune responses, primarily involving the pericardium and pleura. Damage to mesothelial cells and bleeding into the pericardial and pleural spaces cause the production of autoantibodies, which lead to antigen presentation and deposition of immune complexes in the pleuropericardial sac.[1,2] Diagnosis is made clinically by the presence of two of the following; I) fever without alternative causes, II) pericarditic or pleuritic chest pain, III) pericardial or pleural rubs, IV) evidence of PE and/or V) pleural effusion with elevated CRP.[1] PPS is mild in most patients and regresses spontaneously or with anti-inflammatory therapy. NSAID and colchicine are the first line therapy and corticosteroids are used in severe cases, however in case of tamponade or large effusion pericardiocentesis or surgical drainage may be necessary.

In our study we aimed to evaluate the demographic and clinical characteristics of patients who underwent PC due to cardiac surgery related massive PE.

METHODS

The study was conducted with the permission of the Clinical Researches Ethics Committee of Health Sciences University Ankara Pediatrics Hematology Oncology Hospital (Date: 19.04.2019, Decision No: 2019-092). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted in Health Sciences University Dr. Sami Ulus Children Research and Training Hospital, Ankara, Turkiye. We identified 21 children (0-18 years of age) in a 10-year period (2010-2020) for moderate-to-large cardiac surgery related PE relieved by PC and reviewed medical records for demographic and clinical characteristics and management strategies.

Size of the effusion was recorded as maximum diameter between epicardium and pericardium measured during diastole. The presence of signs of tamponade (atrial or ventricular wall collapse etc.) were also determined**.** The amount, color and apperance of fluid obtained by PC was recorded. The results of microbiological (microscopic examination, culture) and biochemical analysis of the fluid was evaluated.

Data were analyzed with a statistical program and descriptive statistics were given as mean±standard deviation, minimum and maximum and percentages. Since it was a retrospective study, informed family consent form could not be obtained.

RESULTS

In the study period 21 patients were enrolled in the study. PC was performed via subxyphoid way in all of the patients.

Demographic and Clinical Findings

Male to female (M/F) ratio was 1.1. Mean age of the patients was 79.7±56.6 months (range btw 4.4-197 months) and the mean body weight (BW) was 19.5±14 kg during PC. Of the patients 6 (28%) were under 3 years of age.

Seven of the patients (33%) had at least one complaint, while the remaining (66.7%) had no complaints and were diagnosed during routine postoperative outpatient clinic control. Considering the presenting complaints, 4 (19%) patients had dyspnea, 2 patients had weakness (8.5%), 1 patient had abdominal pain (4.7%), and 1 patient had fainting (4.7%).

The mean period between cardiac surgery and PC was 30.1±13.4 days. The distribution of surgical indications was as follows; atrial septal defect (ASD) in 9 patients (42.8%), ventricular septal defect (VSD) in 5 patients (23.8%), endocardial cushion defect (ECD) in 2 patients (9.5%), infected thrombus resection, intracardiac mass resection (dystrophic calcification), Fontan operation and ALCAPA in 1 patient (4.7%) each (**Figure**).

Echocardiography, Pericardicentesis and Laboratory Data

The largest diameter of effusion was 34.9±13.4 mm (range btw15-60 mm), and 2.4±1 mm/kg (0.62–6.3 mm/kg) when indexed to BW. Echocardiographic signs of tamponade were present in 6 (28.6%) of the patients. The amount of fluid drained with PC was 349.3±276.1 ml (range btw 65–1400 ml) and 20.8±10.6 ml/kg (range btw 6.6-41.7) when indexed to BW. Macroscopic appearance of the fluid was serous in 6 (28.5%), hemorrhagic in 14 (66.7%) and chylous in 1 (4.8%) patient.

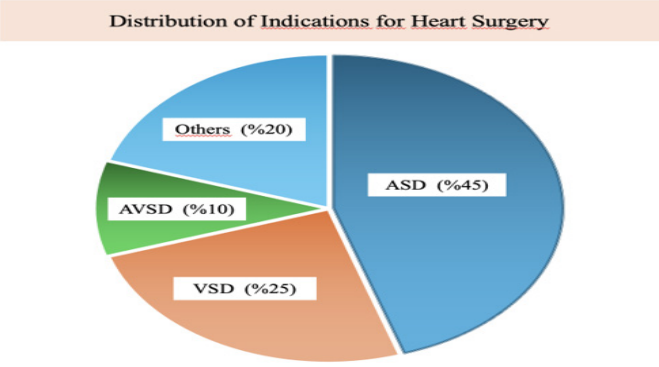

Figure. Indications for heart surgery in patients with PPS and large effusion relieved by PC
ASD: Atrial septal defect, VSD: Ventricular septal defect, AVSD: Atrioventricular septal defect

Laboratuary examination revealed mean erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) value of 23.5mm/hr and 8 mg/L, and elevated in 87.5% and 57.9% respectively. Mean hemoglobin, white blood cell and thromobcyte counts were 12.2±1.92 g/dl, 9.4x106/µl and 327.5x106/µl respectively. Pericardial fluid examination was negative for culture, viral PCR, mycobacterial culture, PCR and ARB.

Management and Outcome

Thirteen of 21 patients were treated with anti-inflammatory drugs; 3 (14.8%) received nonsteroidal anti-inflammatory drugs (NSAIDs), 7 (33.3%) received NSAIDs and colchicine, and 3 (14.8%) received NSAIDs, colchicine, and steroids. Surgical drainage was performed in 1 patient with recurrent effusion that was unresponsive to medical treatment. Ampirical antibiotic theraphy was given in 11 (57.9%) patients. On the follow up, 2 (9.5%) patient died because of sepsis and heart failure. No case of chronic effusion or constriction was observed during follow-up. The characteristics and results of the PPS patients are given in **Table**.

DISCUSSION

PPS is a diagnosis of exclusion characterized by fever, pericarditis and pleuritis. A significant portion of PE developing after cardiac surgery respond to anti-inflammatory treatment, however moderate and severe PE can progress to cardiac tamponade and may require urgent intervention. Relatively slow accumulation of fluid in postoperative patients causes the signs of tamponade to occur later than in patients with non-surgery related effusions. Studies have reported the incidence of PPS and PE as 3-43% and the incidence of tamponade as 1-2%.[6] Cheung et al.[7] followed patients with serial echocardiogram and found that 23% of the patients developed PE and in 13% of them had moderate to large PE. In the study of Elias et al.[6], it was reported that PC was applied in 44.2% of 1535 patients who developed PE after cardiac surgery, while it was reported 7% in an another study.[8] In our study, rate of PC and cardiac tamponade after

Table. The demographic and clinical characteristics of the PPS patients

Characteristics	n	%	Mean±SD	Min.-Max.
Sex				
Male	11	52.4		
Female	10	47.6		
Age (months)			79.7±56.6	4.4 - 197
<3 years	6	28.6		
≥3 years	15	71.4		
Body weight (kg)			19.5±14	3 - 6
Presenting complaint				
None	14	66.7		
At least one	7	33.3		
Echocardiography				
Tamponade	6	28.6		
Max. diameter (mm)			34.9±13.4	15-60
Max. diameter indexed to body weight (mm/kg)			2.4±1	0.62-6.33
Pericardiocentesis				
Post-op interval (day)			30.1±13.4	
Amount of fluid drained (ml)			349.2±276.1	65-1400
Amount of fluid drained indexed to body weight			20.8±10.6	6.6-41.7
Serous	6	28.5		
Hemorrhagic	14	66.7		
Chylous	1	4.8		
Laboratory				
Sedimentation rate (elevated in 87%)			23.5	7-55
CRP (elevated in 57%)			8	3-72
Leukocyte (x10^6/µl)			9.4	5.35 – 23.25
Management				
NSAIDs	3	14.8		
NSAIDs+colchicine	7	33.3		
NSAIDs+colchicine+steroid	3	14.8		
Surgical drainage and tube placement	1	4.8		

Post-pericardiotomy syndrome, SD: Standard deviation, Min: Minimum, Max: Maximum, CRP: C-reactive protein, NSAIDs: Non-steroidal anti-inflammatory drugs

heart surgery were 0.2% and 0.06% respectively. Since only the patients withh severe effusion who underwent PC were included in the study, the overall PE rate was not given.

Among the patients in our study M/F ratio was 1.1. Dalili et al.[8] and Elias et al.[6] found no significant difference in terms of gender, however, Cheung et al.[7] reported female predominance with a M/F ratio of 0.54. When PE and PPS cases developed after cardiac surgery were evaluated, it was reported that female gender was a risk factor for re-admission.[5] In our study, although there was no significant difference in terms of gender, it was observed that the ratio of female sex was relatively increased when compared with the patients who underwent PC for reasons other than cardiac surgery in our center.

PPS is rare under 2 years of age and risk of PE increases with increasing age.[6,9] Elias et al.[6] found that 1535 of 142.633 surgical admissions had readmission for PE and they reported that mean age for patients with PE was significantly higher than that of without PE (24.5 months vs 6.4 years respectively). One study reported the average age of patients developing PPS after ASD surgery as 3.8 years, and another study reported that the risk doubled over the age of 5.[10,11] In a study with adult patients, the risk of PPS was found to be higher at younger ages.[12] This may be explained by a stronger immunological response ability in older children and also for younger adults. In our study, in accordance with the literature, 71.4% of the patients were over 3 years old with a mean age of 6.9 years.

Clinical findings and complaints in PE vary. At the time of admission, at least one complaint was reported in 33.3% of the patients, respiratory distress was found to be the most common. Similarly, in the literature, the rate of complaints was found to be low in patients who developed PE after cardiac surgery. While one study reported the presence of clinical findings as 23% in all patients with PE and 47.4% in those with severe effusion, another study found it to be only 19%.[7,8] Considering the high rate of patients without clinical symptoms and signs in some previous studies, it should be kept in mind that even atypical findings such as fatigue and abdominal pain may be associated with PPS, especially in patients who had undergone cardiac surgery and applied to the outpatient clinic or emergency department.

CRP and ESR are elevated along with neutrophilic leukocytosis in most PPS patients although their specificity is poor during the first weeks after cardiac surgery.[12-14] In the study of Heching et al.[10], laboratory tests were performed in 55% of the patients at the time of diagnosis, and it was reported that 44% had elevated CRP and 37% had elevated ESR. We found leukocytosis in 25%, CRP elevation in 57% and ESR elevation in 87.5% of the patients.

PPS develops after corrective surgeries and also occur after direct or indirect irritation of the pericardium after palliative interventions. In the literature, reported risk factors for PE and PPS after cardiac surgery were; presence of effusion before discharge, female gender, advanced age, use of warfarin, pleural incision, Ross procedure, ASD, valve operation, Fontan operation, AVSD, Blalock-Taussig shunt, heart transplantation Trisomy-21, winter and summer months, low platelet values, high lymphocyte values, low interleukin-8 levels, erythrocyte transfusion and renal failure.[2,5-8,15] In our study indication for heart surgery was ASD in 9 (42.8%) of 21 patients. The cause of PE in patients after ASD operation is thought to be due to the change in mechanical properties as a result of chronic exposure of the right atrium with pericardiotomy and right atriotomy. Elias et al.[6] reported that the response to medical treatment is less in PE related to ASD operation. Trisomy-21 is previously reported as a risk factor for PE, and hypothyroidism and abnormal myelopoesis were suggested as the cause of predisposisiton.[15-17]

Although PPS is typically seen in the first weeks after surgery, it can develop months after the operation. Dalili et al.[8] reported that PE developed in 87% of the patients within the

first 13 days after the operation and Cheung et al.[7] reported in 97% of the patients in the first 28 days after surgery. In our study, the mean interval between cardiac surgery and PC was 30.1±13.4 days (6-60 days) in line with the literature. For our patients, it was observed that the patients were advised for outpatient control at the end of first month. Considering that a significant portion of our patients who underwent PC for PPS did not report any complaints at the first control, it would be more appropriate to perform routine cardiology outpatient controls at shorter intervals after the surgical procedure.

Although it is important to evaluate the amount of fluid, of it should be noted that there is no correlation between the amount of fluid and clinical findings. In our study, the amount of effusion was evaluated by taking the largest diameters measured in diastole. Due to the different age groups and body weights of the patients, these measurements were also evaluated by proportioning their body weight. In patients with surgery related PE "Pediatric tamponade index (PTI) (amount of fluid drained for 24 hours with the inserted chest tube to body weight)" was defined and it was reported that, PTI>21were related with more severe clinical findings, longer hospital stay after PC and need for inotropic support before the procedure.[18]

For the treatment of PPS use of NSAIDs and colchicine, with the occasional addition of corticosteroids is recommended according to ESC guidelines.[1] It has been reported that there was no significant difference in the incidence of PPS in patients who were given short-term prophylactic methylprednisolone and acetylsalicylic acid treatments compared to the group that was not given.[19,20] In another study, it was reported that the incidence of PPS was statistically significantly lower at the end of 1 year in patients receiving prophylactic colchicine.[21] The use of ibuprofen or indomethacin for 10 days has been reported to relieve symptoms and shorten the duration of illness without causing significant side effects.[22] Giacinto et al.[23] reported a better outcome when colchicine and indomethacin were administered as primary prophylactic agents and Malektori et al.[24] recommend colchicine use to reduce the risk of the PPS. None of the patients in our study received prophylactic treatment.

In our center, subxiphoid percutaneous PC and/or pericardial catheter placement with a subxiphoid percutaneous approach is preferred. Minimally invasive surgical intervention is also preferred in some centers, and it is claimed to have advantages such as direct visualization of the pericardium and heart, opening of pericardial adhesions, and opening of the pericardial window when necessary.[18] Fields et al.[25] found no differences in efficacy, safety, and resource utilization between initial drainage through pericardial window compared to pericardiocentesis in children with PPS warranting fluid drainage. No serious complication related to the procedure was observed and the success of the procedure was high in our study. We think that surgical intervention is more appropriate in patients who require a pericardial window due to the locality of the effusion, the presence of widespread fibrous structures and the recurrent effusions.

Limitations

The retrospective nature of the study, the inclusion of only patients who underwent PC, and the inability to compare the initial clinical and laboratory findings with the results were considered limitations of the study.

CONCLUSION

PPS is an important post-operative complication and may cause significant consequences such as tamponade, requiring PC or surgical drainage. Considering that a significant portion of our patients who underwent PC for PPS did not report any complaints at the first control, it would be more appropriate to perform routine cardiology outpatient controls at shorter intervals after the surgical procedure especially in case of presence of reported risk factors. In patients unresponsive to medical treatment percutaneous PC is a safe and effective method along with anti-inflammatory drugs.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Clinical Researches Ethics Committee of Health Sciences University Ankara Pediatrics Hematology Oncology Hospital (Date: 19.04.2019, Decision No: 2019-092).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of
Cardiology & Cardiovascular
Surgery

DOI: 10.51271/JCCVS-0051

Letter to the
Editor

Comment on "Concomitant pulmonary thromboendarterectomy and supracoronary ascending aorta replacement: case report"

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Cite this article: Özbakkaloğlu A. Comment on "Concomitant pulmonary thromboendarterectomy and supracoronary ascending aorta replacement: case report". *J Cardiol Cardiovasc Surg.* 2025;3(1):19-20.

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Received: 17/12/2024 ◆ **Accepted**: 17/03/2025 ◆ **Published**: 27/03/2025

Keywords: Pulmonary thromboendarterectomy, chronic thromboembolic pulmonary hypertension, ascending aorta replacement

Dear Editor,

I have read the case report of Concomitant pulmonary thromboendarterectomy and supracoronary ascending aorta replacement by Osman Fehmi Beyazal, et al. with great interest. The limitations and advances of the case are clearly discussed by the authors. It is very promising to know that highly equipped surgical teams that can perform this kind of complex surgeries with great outcomes exist. The preoperative evaluation of the patient was done significantly, and all possible results were measured. All indications for combined surgery were made clear by the authors prior to intervention. I believe that postoperative outcomes were also made very clear.

I would like to ask the authors why postoperative transthoracic echocardiography (TTE) at 3 months was not included in the report.[1] In both preoperative and postop 7th day TTE, TAPSE was measured 19 mm and 12 mm consecutively which indicates poor prognosis. In early stages after pulmonary thromboendarterectomy (PTE) TAPSE was found to decrease in literature[2] however it does not correlate with pulmonary valve resistance (PVR) after surgery that is why adding long term follow-up TTE results will bring more insight to the reader and might enlighten more issues in this subject. Another issue is that an patent foramen ovale (PFO) was mentioned in the first preoperative TTE but was not mentioned on the 2nd and postoperative TTE. This raises the question "What happened to the PFO?". In case of deep vein thrombosis (DVT) PFO can cause paradox embolism, and I believe that the patient can also benefit from PFO closure during cardiac surgery. Addition of a late stage postoperative TTE will eliminate these questions from a great deal of readers.

Once again, I would like to congratulate and thank the authors for their great work.

ETHICAL DECLARATIONS

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Author reply "Concomitant pulmonary thromboendarterectomy and supracoronary ascending aorta replacement: case report"

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Dear Editor,

Patent foramen ovale (PFO) was detected in transthoracic echocardiography (TTE) performed when the patient applied to the cardiology clinic and thrombolytic treatment was initiated. As mentioned in our article, no PFO findings were observed in the TTE performed two years later, when the patient applied to us.[1] Therefore, there was no need for surgical intervention. Indeed, PFO was not observed in any of the many postoperative control TTEs. Additionally, PFO was not observed in the postoperative right heart catheterization (RHC). This difference between the initial TTE and subsequent TTE findings may be due to false positivity in the initial TTE, or it may be due to spontaneous closure that significantly reduced contrast transmission in the 2-year period. In the latest TTE performed 16 months after the operation, the ejection fraction was 50% and TAPSE was 16 mm. In the RHC 17 months later, sPAP was measured as 30 mmHg, mPAP was 22 mmHg, PVR was 3.4 W, cardiac output was 4.4 L/min, and cardiac index was 2.09 L/min/m^2. These findings also show that these values decreased dramatically after the operation compared to the pre-operative values.

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