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Chronotropic incompetence in coronary slow flow

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ABSTRACT

Aims: Previous studies have associated coronary slow flow (CSF) and chronotropic incompetence (CI) with increased mortality. There is no established treatment protocol for CSF. In this study, we aimed to answer questions such as "Is there CI in patients with CSF? If so, is there an increase in the frequency of hospital admissions due to cardiac complaints in these patients?"

Methods: The study included 29 patients with CSF detected according to thrombolysis in myocardial infarction (TIMI) frame count during angiography and 27 healthy volunteers with normal coronary artery as a healty group. The relationship between coronary slow flow and chronotropic incompetence between the patient and healthy healty groups and the differences between these and healty individuals were compared.

Results: The maximum heart rate reached during the treadmill exercise test was found to be statistically significantly lower in patients with coronary slow flow compared to the healty group (p=0.045). The presence of chronotropic incompetence in the patient group with coronary slow flow was found to be statistically significantly higher than the healty group (p=0.038). However, there was no significant difference between the chronotropic indexes (p=0.953). Duke treadmill scores (DTS) were found to be similar between the groups (p>0.05).

Conclusion: Patients with coronary slow flow were found to have statistically significant higher chronotropic incompetence in the treadmill exercise test. However, no significant difference was observed between the groups in the chronotropic index values, which are an indicator of chronotropic incompetence. These results suggest the presence of autonomic dysfunction in coronary slow flow phenomenon and that chronotropic incompetence may be caused by coronary slow flow phenomenon and should be investigated in etiology.

Keywords: Coronary slow flow, chronotropic incompetence, treadmill exercise test, chronotropic index

INTRODUCTION

The coronary arteries provide blood flow to the heart, along with the supply of nutrients and oxygen. This allows the heart to pump blood to itself and to the circulatory system in our body. Coronary slow flow was defined by Tambe et al.[1] as the delay in the passage of contrast material to the distal part of the epicardial coronary arteries angiographically.[1] It is known as cardiac syndrome Y. Patients with slow coronary flow may experience recurrent chest pain at rest or with exercise. Many patients with slow coronary flow undergo index diagnostic angiography after the onset of acute coronary syndrome and electrocardiographic changes. The incidence in patients with chest pain undergoing diagnostic catheterization is 1-7%.[1] In conclusion, recurrent angina in patients with slow coronary flow causes frequent hospital readmissions and poor quality of life. Mortality in patients with slow coronary flow is reportedly approximately <1%.[2] Slow coronary flow is more common in men, smokers, obese and young patients. It is known that both systolic and diastolic functions are impaired in patients with slow coronary flow according to the data obtained from echocardiographic imaging.[2] Slow coronary flow has been reported to be associated with life-threatening arrhythmias and sudden cardiac death, and it has been thought that this may be due to increased QTc dispersion.[3] In clinical practice, coronary flow assessment is performed by the semi-quantitative method of TIMI flow grading or quantitatively by the TIMI Frame counting (TFC) method.[4] TIMI frame count system and myocardial perfusion degree are angiographic markers of the effectiveness of coronary reperfusion at the epicardial artery and microcirculation levels.[5] Coronary slow flow is diagnosed by the absence of ≥40% angiographic stenosis, TIMI-2 flow in at least one epicardial coronary artery (≥3 beats required to opacify the vessel) or TFC >27 frames (in images obtained at 30 frames/sec).[6] Quantitatively, a TFC measurement corrected for all coronary arteries >27 frames are considered diagnostic of CSF. The LAD has been reported to be 1.7 times longer than the TIMI frame count (36.2±2.6 frames), RCA mean (20.4±3.0 frames), and CX artery counts (22.2±4.1 frames). A correction factor of 1.7 is used for the LAD.[4] The LAD is the most affected vessel. However, multivessel involvement represents more severe, widespread disease and may be a sign of poorer prognosis.[1] The exact etiology and pathogenesis of coronary slow flow are unclear. Furthermore, many questions remain as to whether this pathology is limited to the coronary arteries or is a manifestation of systemic vascular disease. Multiple causes

have been suggested, including endothelial dysfunction, small vessel disease, microvascular dysfunction, morphological and functional abnormalities of blood cells, metabolic disorders, increased inflammation, and latent atherosclerosis.[7,8] Various theories have been used to explain the pathogenesis of coronary slow flow, but there are still unanswered questions that will require longer series and new studies to resolve. Since the etiology of coronary slow flow has not been fully elucidated, there is no clear treatment. Treatments are applied for symptoms and risk factors such as hypertension and diabetes mellitus. Heart rate at any given moment reflects the balance between the sympathetic and parasympathetic autonomic nervous systems.

Resting heart rate (HR) in humans is usually much lower (60–80 beats/min) because of the dominant influence of the vagus nerve. Chronotropic incopotency is generally defined as the failure of the heart to increase its rate in proportion to increased activity or demand. It is common in patients with cardiovascular disease, causing exercise intolerance that impairs quality of life. It is an independent predictor of major adverse cardiovascular events and overall mortality.[9] However, the importance of chronotropic incopotency is underappreciated and is often overlooked in clinical practice, in part because of its vague definition, the possible dependence on aging, the confounding effects of medications, and the need for formal exercise testing for definitive diagnosis. The association between chronotropic incopotency and increased cardiac and all-cause mortality was first reported more than 30 years ago by Hinkle and colleagues.[10] Ellestad and colleagues confirmed an increased risk of cardiac events after long-term follow-up of patients with this phenomenon.[11]

Treadmill exercise testing indirectly detects myocardial ischemia, which is the physiological consequence of a mismatch between myocardial oxygen delivery (coronary blood flow) and myocardial oxygen demand.[12] In general, Treadmill exercise testing is evaluated by three main parameters: clinical symptoms and signs (chest pain, low exercise capacity); electrocardiography (ECG) abnormalities (ST segment abnormalities, arrhythmias); and hemodynamic response (exercise-induced hypotension).[13] Inability to exercise for >6 minutes on the Bruce protocol in the treadmill exercise test or inability to increase heart rate to >85% of age-expected heart rate are important indicators of increased risk of coronary events, with 5-year survival rates ranging from 50% to 72%. Heart rate changes, both during and after exercise, are strong predictors of sudden death in asymptomatic and selected clinical populations, including those with coronary artery disease or heart failure.

Chronotropic incopotency is most commonly diagnosed by failure of the heart rate to reach 85% of the age-expected heart rate. The chronotropic index is defined as an indicator of heart rate reserve. Azarbal et al.[14] showed that a low heart rate reserve percentage was a superior predictor compared with failure to reach 85% of the age-expected heart rate, as the latter method identified 2.2 times more individuals at increased risk of cardiac death.

In this study, we aimed to find answers to questions such as "Is there chronotropic incopotency in patients with slow coronary flow? If so, is there an increase in the frequency of hospital admissions with cardiac complaints in these patients?"

METHODS

Ethics

The study was conducted with the permission of the Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 22.02.2023, Decision No: 2023/02).

Study Design and Patient Selection

The study was designed as a retrospective cross-sectional study. Individuals aged 18 years and older who were evaluated in the outpatient clinic between 2021-2023 with complaints such as chest pain and shortness of breath were invited to participate in the study. After the objectives of the study were explained and written consent was obtained from the patients, the basic characteristics and clinical data of the participants were recorded. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later amendments or comparable ethical standards.

Patients who applied with anginal complaints such as chest pain and shortness of breath, who underwent 12-lead ECG, echocardiography and blood tests, and then underwent exercise testing and coronary angiography as advanced tests were included in our study. Patients aged 18 years and over were included in the study. Patients under the age of 18, with serious heart valve diseases such as aortic stenosis, severe mitral regurgitation or mechanical prosthetic heart valves, Patients with severe structural or congenital heart disease, Patients with previously diagnosed coronary artery disease (CAD) or a history of coronary bypass surgery by angiography, Patients with arrhythmia and permanent pacemakers, pulmonary hypertension, patients with chronic renal failure, severe liver dysfunction, primary pulmonary pathology, pregnant women and BMI>35kg/m^2 were excluded from the study. A total of 29 patients with TIMI frame counting detected according to TIMI frame count during angiography were included in this study. The healthy healty group consisted of 27 healthy individuals who applied to the cardiology clinic with similar complaints and who did not have any other disease that could be included in the exclusion criteria and who had normal coronary angiography

Cardiovascular Examination and Blood Tests

All patients and healthy individuals included in the study were first recorded for demographic characteristics and general systemic examinations were performed. Height, weight and body-mass index (BMI) were recorded. After physical examination, ECG, lipid panel, thyroid function tests, electrolytes, kidney function tests, liver function tests, biochemical tests including hormones and hemogram examination were performed. Echocardiography and treadmill exercise tests were performed for complaints of patients and healthy individuals. Coronary angiography was performed electively via femoral or radial access after written consent was obtained from patients for whom coronary angiography was decided as a result of physical examination and examinations.

Echocardiography

The echocardiography data of the patients and healthy individuals used in our study were obtained from the data storage of the GE (General Electric Company, Indianapolis,

Indiana USA) Vivid E9 device in the echocardiography laboratory and from the hospital information management system where patient data is stored.

Treadmill Exercise Test

It was performed in our laboratory with the GE CASE exercise testing system brand treadmill exercise device in accordance with the Bruce protocol and accompanied by an experienced nurse. The medications of patients using anti-ischemic drugs were stopped 48 hours before the test. The test was performed without the effect of any drug. Typical angina pectoris that limits effort, horizontal or downward-sloping ST depression of 1 mm and above, and insufficient increase or decrease in blood pressure contrary to expectations were taken as positivity criteria. Tests with suspicious chest pain, not reaching the expected target heart rate according to age, showing ST changes that did not meet the positivity criteria or having low diagnostic value due to baseline ECG changes were considered suspicious/possible positive. The patients' initial heart rates and maximum heart rates were measured. The expected heart rate according to age was calculated with the formula 220-age.[12]

The presence of chronotropic insufficiency in patients was accepted as not reaching 80% of the expected heart rate according to age. Heart rate reserve was calculated as the change in heart rate from the resting time to the peak exercise time during the exercise test. chronotropic index is obtained by dividing the change in HR from the resting time to the peak exercise time by the difference between the resting HR and the age-expected heart rate.[12] We also used this formula in our study.

KI=(HR peak-HR resting)/(Age-expected heart rate-HR resting)x100 Duke treadmill score (DTS) was calculated. Patients with a treadmill score ≥5 were classified as low risk, those between -10 and 4 as moderate risk, and those with a treadmill score below -10 as high risk. DTS was calculated using the following formula: DTS= Exercise duration (min)-(5xmaximum ST segment deviation)-(4xangina score)

Coronary Angiography

All cases underwent selective right and left coronary angiography using the GE optima CL323i device using the femoral or radial artery approaches. Coronary arteries were imaged in standard positions at least 5 using right and left oblique, cranial and caudal angles. TIMI frame counting method was used to determine the presence of coronary slow flow.[4] The frame where the contrast material entered the coronary artery was accepted as the first frame. The last frame was determined according to the literature according to the coronary artery. The distal bifurcation called whisker for LAD, the distal bifurcation of the longest responsible branch for CX, and the frame where the first side branch of the posterolateral artery (PL) emerged for RCA were determined as the last frame. An average of 6–8 ml of contrast material was injected for each exposure. Coronary arteries were imaged at a speed of 15 frames/sec. While making calculations, adjustments were made to a speed of 30 frames/sec. In addition, the corrected LAD TIMI frame count was obtained by dividing the LAD frame count by 1.7. A TIMI frame count of >27 without stenosis or obstruction in one or more coronary arteries was evaluated as the presence of coronary slow flow phenomenon.[15]

Statistical Analysis

The data obtained as a result of the research were analyzed in a computer environment using SPSS (Statistical Package for Social Sciences) 18.0 package program. In descriptive analyses, frequency data were shown as number (n) and percentage (%), and numerical data were shown using mean±standard deviation. Chi-square (X^2) test and Fisher's exact chi-square test were used to compare categorical data. The conformity of numerical data to normal distribution was examined using the Kolmogorov-Smirnov test. The distribution of normally distributed numerical data in two independent groups was evaluated with the independent samples T test, and the distribution of non-normally distributed numerical data was evaluated with the Mann Whitney U test. The level of statistical significance was accepted as $p<0.05$ for all tests.

RESULTS

This study included 29 patients who were evaluated with complaints of chest pain and shortness of breath in the cardiology outpatient clinic of Kırıkkale University Faculty of Medicine and who were diagnosed with slow coronary flow by laboratory tests, electrocardiography, echocardiography, treadmill exercise test and then coronary angiography, and 27 healthy volunteers who were diagnosed with normal coronary arteries. 75.9% (22 patients) of the patients with slow coronary flow were male and 24.1% (7 patients) were female. In the healty group, 51.9% were male (14 patients) and 48.1% (13 patients) were female. The mean age of the patient group with slow coronary flow was 52.17±9.13; the mean age of the healty group was 49.14±8.65.

The comparison of all individuals included in the study as patient and healty groups is shown in **Table 1**. Hypertension was present in 12 patients (41.4%) in the patient group with slow coronary flow, while it was present in 4 patients (14.8%) in the healty group. The mean BMI and hypertension rate were found to be statistically significantly higher than in the healty group (p values; p=0.015, p=0.039, respectively). While 2 of 29 patients (6.9%) with slow coronary flow presented with angina in the first 6 months, 3 of 27 patients (11.1) in the healty group presented. No significant difference was found between the groups in presentations due to angina in the first 6 months. In the patient group with detected coronary slow flow, left atrium (LA) diameter, left ventricular (LV) end-diastolic and end-systolic diameters, LV end-diastolic volume, LV systolic mass were found to be statistically significantly higher than the healty group (p values; p=0.041, p=0.034, p=0.014, p=0.022, respectively).

Among patients with slow coronary flow, 79.3% (n=23) were detected in the LAD, 51.7% (n=15) in the Cx, and 69.0% (n=20) in the RCA artery. In the patient group with slow coronary flow, RCA TIMI frame average was 39.37±22.36, CX TIMI frame average was 40.34±25.93, LAD TIMI frame average was 48.73±19.07. In the healty group, RCA TIMI frame average was 19.03±6.50, CX TIMI frame average was 20.29±4.98, LAD TIMI frame average was 20.92±5.09. In the patient group with CFA, RCA, CX, LAD measurements were found to be statistically significantly higher compared to the healty group (p values; p<0.001, p<0.001, p<0.001, respectively). No statistically significant correlation was found between chronotropic index and RCA, CX and LAD measurements in patients with slow coronary flow (p>0.05).

In the treadmill exercise test results, while the average METs was 9.35±2.83 in the group with coronary slow flow, it was 9.84±2.47 in the healty group. While the average heart rate before exercise in the group with coronary slow flow was

Table 1. Comparison of the groups in terms of age, gender, smoking, BMI, HT, and re-admission to the hospital within the first 6 months

	Coronary slow flow group (n=29)	Control healty group(n=27)	p value
Age, mean ±SD	52.17±9.13	49.14±8.65	0.209
Gender, n (%)			
Male	22 (75.9)	14 (51.9)	0.061
Female	7 (24.1)	13 (48.1)	
Smoking, n (%)			
No	17 (58.6)	21 (77.8)	0.158
Yes	12 (41.4)	6 (22.2)	
BMI, mean ±SD (kg/m²)	29.35±3.38	27.21±2.91	**0.015**
HT, n (%)			
No	17 (58.6)	23 (85.2)	**0.039**
Yes	12 (41.4)*	4 (14.8)	
Re-admission to the hospital within the first 6 months, n (%)			
No	27 (93.1)	24 (88.9)	0.664
Yes	2 (6.9)	3 (11.1)	
Ekhocardiography			
EF (Teich) %	60.57±4.02	61.62±6.41	0.469
LA-DIA cm	3.40±0.39	3.16±0.44	**0.041**
LVIDd cm	4.62±0.50	4.23±0.79	**0.034**
LVIDs cm	3.12±0.37	2.82±0.48	**0.014**
EDV ml	100.10±24.73	85.48±20.96	**0.022**

*: Group from which the difference originates, BMI: Body-mass index, SD: Standard deviation, HT: Hypertension, EF: Ejection fraction, EDV: External ventricular drainage

83.82±12.87, it was 86.11±11.33 in the healty group. While the average maximum heart rate in the group with coronary slow flow was 83.82±12.87, it was 86.11±11.33 in the healty group. Maximum heart rate was statistically significantly lower in patients with coronary slow flow compared to the healty group (p=0.045). In the patient group with coronary slow flow included in the study, the presence of chronotropic insufficiency was found to be statistically significantly higher than in the healty group (p=0.038) (**Table 2**). However, no significant difference was found between the groups in chronotropic incopotency values, which are accepted as an indicator of chronotropic insufficiency. No statistically significant difference was found between the chronotropic index, chronotropic incopatency and hypertension according to the presence of diastolic dysfunction (p>0.05).

DISCUSSION

Despite numerous studies on coronary slow flow, no consensus has been reached on diagnosis, treatment, and clinical significance of the phenomenon.[16] The relationship between coronary slow flow and chronotropic incopotency and increased mortality has been previously demonstrated. There is no definitive treatment protocol for the coronary slow flow phenomenon.

Beltrame et al.[17] also reported that slow coronary flow is most commonly seen in young men, smokers, and patients presenting with acute coronary syndrome. Similarly, Hawkins et al.[15] predicted male gender and obesity as independent risk factors for the presence of slow coronary flow in their study. In contrast, Yılmaz et al.[18] reported that no statistically significant difference was found between the groups in terms of age, gender, hypertension and smoking frequency, while they reported that the incidence of metabolic syndrome increased in patients with slow coronary flow. Similarly, in the study conducted by Doğan et al.[19] no significant difference was found between the patients with slow coronary flow and the healty group in terms of age, gender, presence of HT, smoking status and lipid levels. In our study, no difference was found between the groups in terms of age, gender and smoking. However, BMI and the presence of HT were found to be statistically significantly higher in the slow coronary flow group compared to the healty group. In our study, there was a numerical difference between gender and smoking, but we think that the lack of statistical difference may be due to the small number of patients. The results of these data may vary with increasing the number of patients included in the study.

In a study conducted by Sanghvi et al.[20] hypertension, dyslipidemia and smoking were identified as independent determinants of coronary slow flow, and the most common symptom was presentation with acute coronary syndrome. In addition, a relationship was identified between coronary slow flow and increased insulin resistance and glucose intolerance.[21] Binak et al.[22] did not find any difference between fasting plasma lipid and glucose levels in their study, but they stated that there was a relationship between glucose intolerance and coronary slow flow in their study. These studies indicate that there is

Table 2. Comparison of groups in terms of failure to reach 80% of age-expected heart rate, chronotropic index, Duke treadmill score

	Coronary slow flow group (n=29)	Control healty group (n=27)	p value
Terms of failure to reach 80% of age-expected heart rate			
No	19 (65.5)	24 (88.9)	**0.038**
Yes	10 (34.5)*	3 (11.1)	
Chronotropic index (CI), mean ±SD	0.67±0.23	0.67±0.15	0.953
CI			
Normal	12 (41.4)	6 (22.2)	0.125
Abnormal	17 (58.6)	21 (77.8)	
DUKE, n (%)			
Low risk	14 (48.3)	18 (66.7)	0.165
Medium risk	15 (51.7)	9 (33.3)	
Duke treadmill score (DTS), mean ±SD	3.76±4.98	4.73±3.77	0.417

*: Group from which the difference originates, SD: Standard deviation

a relationship between coronary slow flow and metabolic syndrome. In our study, we did not find any significant difference between lipid profiles and glucose values. We think that this difference may be due to the exclusion of diabetic and chronic disease patients from our study.

Beltrame et al.[17] reported that more than 80% of patients experienced recurrent chest pain; almost 20% of the affected patients required re-admission to the coronary care unit. In our study, we found that there was no difference in the presentation to our clinic due to recurrent chest pain between the groups during the first 6 months of follow-up. We attributed the lack of difference between the groups to the short follow-up period, the small sample size, and the possibility that the patients presented to different clinics.

While there are studies indicating that LV ejection fraction is normal in slow coronary flow, there are also studies detecting LV systolic and diastolic dysfunction in patients with slow coronary flow.[23,24] Sezgin et al.[25] also reported diastolic filling abnormalities in patients with coronary slow flow and demonstrated diastolic dysfunction. In our study, there was no significant difference in LV ejection fractions. We think that this may be due to the exclusion of patients with heart failure and moderate-severe valvular functional disorders from our study. Narimani et al. found significant differences between the groups in LVESD, LVEDD, EF, E waves, A waves, E/A ratio, DT and IVRT. They also reported that the lateral wall E and S waves were lower in these patients.[26] In our study, values such as LV end-diastolic and end-systolic diameters, LV end-diastolic volume, LV systolic mass were found to be statistically significantly higher in patients with slow coronary flow compared to the healty group. In the study conducted by Shui et al.[27] it was determined that the left atrial diameter was increased and the left atrial functions were impaired in patients with slow coronary flow. In our study, the left atrial diameter was found to be statistically significantly higher in patients with slow coronary flow compared to the healty group. However, due to the retrospective design of our study, we could not evaluate the LA functions of our patients in detail.

In our study, as in other studies, the artery with the most common slow coronary flow was the LAD. However, there are other studies in which the LAD was not most frequently involved.[28,29]

Elsherbiny et al.[30] in their study, found that patients with slow coronary flow had weaker peak exercise capacity than healties, and that there was a significant negative correlation with the mean TIMI frame count. They emphasized that there was deterioration in LV systolic and diastolic functions, which had a clinical effect on exercise capacity in patients with slow coronary flow, and that this situation was important for risk stratification and close follow-up of these patients.[30] In contrast, in the study conducted by Tekin et al.[31] no significant difference was observed between the slow coronary flow and healty groups in terms of maximum heart rates and METs at rest and during exercise. However, a decrease in heart rate recovery in the first minute was observed in patients with slow coronary flow. They suggested that decreased vagal activity may be responsible for slow coronary flow.[31] In the study by Aşkın et al.[32] which examined the relationship between heart rate recovery and coronary slow flow, no significant difference was observed between maximum HR at rest and during exercise and METs; however, HR recovery at the 1st, 2nd, 3rd and 5th minutes was found to be significantly lower in patients with coronary slow flow. In our study, there was no significant difference between resting heart rates and METs. However, maximum heart rates were significantly lower in the coronary slow flow group. In their study comparing stable CAD and healty groups, Chen et al.[33] found that heart rate recovery values and heart rate recovery change parameters were significantly lower in the stable CAD group compared to the healty group, and suggested that this suggested the presence of autonomic dysfunction in stable CAD patients. In particular, they found that delayed heart rate recovery and reduced heart rate variability were associated with stable CAD, while low heart rate recovery values were associated with severe coronary lesions in stable CAD patients. They suggested that the risk of stable CAD increased in patients with abnormal heart rate recovery and heart rate variability, and that abnormal heart rate recovery could be used to predict the severity of coronary lesions.[33] In our study, the number of patients with abnormal heart rate recovery in the first minute was higher in the coronary slow flow patient group, but no statistically significant difference was observed (p=0.052). These results suggest that the data may differ by increasing the number of patients in the study.

Youn et al.[34] investigated the relationship between coronary flow reserve and Duke treadmill score (DTS) in patients with microvascular angina, and examined 108 patients with chest pain and normal coronary angiography, and concluded that DTS is an index that reflects coronary flow reserve and helps clinicians determine the severity of ischemia in patients with microvascular angina. A statistically significant positive correlation was found between Duke treadmill score and coronary flow reserve in the study.[34] In our study, no significant difference was found between the duke treadmill scores of the patients included in the study. We thought that this could be due to the fact that our patients were not high-risk patients.

In the study conducted by Anjos et al.[35] which included patients with suspected coronary artery disease, the frequency of chronotropic incopotency was determined as 15.9%, and it was shown that the prevalence of symptoms and coronary risk factors was higher in the chronotropic incopotency group. In the study, patients with chronotropic incopotency exhibited lower heart rates at rest and during maximum exercise in the treadmill exercise test. They found that structural and ischemic abnormalities were more common in echocardiographic evaluations of patients with chronotropic incopotency. They also stated that chronotropic incopotency was associated with left ventricular dysfunction during intense exercise and was a marker of ischemia and severe coronary artery disease, and suggested that chronotropic incopotency was associated with critical right coronary artery lesions.[35] Similar to these results, in our study, a statistically significant difference was found in echocardiography findings and target heart rate values according to age in patients with slow coronary flow.

In a study comparing heart failure patients with preserved EF and healties, in which the mechanism of chronotropic insufficiency was tried to be explained, and in which exercise test and graded isoproterenol infusion were applied to measure cardiac beta receptor-mediated heart rate responses, it was stated that heart failure patients with preserved EF exhibited impaired cardiac beta receptor sensitivity compared to healties. The researchers stated that this could be due to increased plasma isoproterenol concentrations in HF patients with preserved EF and blunted heart rate response despite exercise, which could

be due to decreased sinus node beta receptor sensitivity.[36] In our study, no statistically significant difference was found between chronotropic index, chronotropic incopotency and HT presence according to the presence of diastolic dysfunction (p>0.05). We thought that this situation could be due to the small number of our patients, low mean age, and exclusion of diabetic patients and patients with BMI>35kg'm^2 from the study.

In our study, we conducted a study by calculating both the patients' failure to reach 80% of the expected heart rate according to age and the chronotropic index values. Chronotropic incopotency was observed statistically at a higher rate in the coronary slow flow group (p<0.05). The maximum heart rates of these patients were lower than in the healty group (p<0.05). However, we found that there was no significant difference between the groups in CI values, which are an indicator of HF and are thought to be superior in showing the presence of HF. Regardless of how HF is evaluated, an impaired chronotropic response is believed to partially reflect an underlying abnormality in autonomic nervous system function and has been associated with cardiovascular events.[37]

CONCLUSION

Although coronary blood flow is regulated by neurohumoral, endothelial, and metabolic factors, the pathophysiology of coronary slow flow has not been fully elucidated. It has been reported that there may be deterioration in LV systolic and diastolic functions in these patients and that coronary slow flow has an effect on exercise capacity. Since coronary slow flow causes frequently recurring anginal symptoms and neurohumoral factors are also thought to be effective in its etiopathogenesis, this study suggests that there may be chronotropic incopotency, which is frequently seen in the community and thought to be a result of autonomic dysfunction. Some data in our study may indicate the presence of autonomic dysfunction in coronary slow flow. However, new studies involving more patients are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 22.02.2023, Decision No: 2023/02).

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.

REFERENCES

1. Zavala-Alarcon E, Cecena F, Little R, Bant A, Van Poppel S, Patel R. The no-flow phenomenon during diagnostic coronary angiography. *Cardiovasc Revasc Med*. 2005;6(3):126-132.
2. Barutcu I, Sezgin AT, Sezgin N, et al. Increased high sensitive CRP level and its significance in pathogenesis of slow coronary flow. *Angiology*. 2007; 58(4):401-407.
3. Atak R, Turhan H, Sezgin AT, et al. Effects of slow coronary artery flow on QT interval duration and dispersion. *Ann Noninvasive Electrocardiol*. 2003; 8(2):107-111.
4. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation*. 1996;93(5):879-888.
5. Group TS. *TIMI definitions for commonly used terms in clinical trials*. 2009.
6. Beltrame JF. Defining the coronary slow flow phenomenon. *Circ J*. 2012; 76(4):818-820.
7. Kalay N, Aytekin M, Kaya MG, et al. The relationship between inflammation and slow coronary flow: increased red cell distribution width and serum uric acid levels. *Turk Kardiyol Dern Ars*. 2011;39(6):463-468.
8. Kuyumcu MS, Kuyumcu A, Yayla Ç, et al. Nesfatin-1 levels in patients with slow coronary flow. *Kardiol Pol*. 2018;76(2):401-405.
9. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation*. 2011;123(9):1010-1020.
10. Hinkle LE Jr, Carver ST, Plakun A. Slow heart rates and increased risk of cardiac death in middle-aged men. *Arch Intern Med*. 1972;129(5):732-748.
11. Ellestad MH, Wan MK. Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing. *Circulation*. 1975; 51(2):363-369.
12. Chareonthaitawee P, Askew JW, Pellikka PA. *Exercise ECG testing: performing the test and interpreting the ECG results*. PA Pellikka (Ed.), TF Dardas(Ed.), Uptodate. https://www. uptodate.com/contents/exercise-ecg-testing-performing-the-testand-interpreting-the-ecgresults, 2020.
13. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. 1990;13(8):555-565.
14. Azarbal B, Hayes SW, Lewin HC, Hachamovitch R, Cohen I, Berman DS. The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: superiority over 85% of maximal age-predicted heart rate. *J Am Coll Cardiol*. 2004;44(2):423-430.
15. Hawkins BM, Stavrakis S, Rousan TA, Abu-Fadel M, Schechter E. Coronary slow flow--prevalence and clinical correlations. *Circ J*. 2012;76(4):936-942.
16. Yilmaz M, Dağli MN. Koroner yavaş akım. *Fırat Üniversitesi Sağlık Bilimleri Tip Dergisi*. 2016;30(3): p.147-152.
17. Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon--a new coronary microvascular disorder. *Cardiology*. 2002;97(4):197-202.
18. Yilmaz H, Demir I, Uyar Z. Clinical and coronary angiographic characteristics of patients with coronary slow flow. *Acta Cardiol*. 2008;63(5): 579-584.
19. Dogan SM, Yildirim N, Gursurer M, Aydin M, Kalaycioglu E, Cam F. P-wave duration and dispersion in patients with coronary slow flow and its relationship with thrombolysis in myocardial infarction frame count. *J Electrocardiol*. 2008;41(1):55-59.
20. Sanghvi S, Mathur R, Baroopal A, Kumar A. Clinical, demographic, risk factor and angiographic profile of coronary slow flow phenomenon: a single centre experience. *Indian Heart J*. 2018;70 Suppl 3(Suppl 3):S290-S294.
21. Ozcan T, Gen R, Akbay E, et al. The correlation of thrombolysis in myocardial infarction frame count with insulin resistance in patients with slow coronary flow. *Coron Artery Dis*. 2008;19(8):591-595.
22. Binak E, Gunduz H, Sahin M, Kurtoglu N, Dindar I. The relation between impaired glucose tolerance and slow coronary flow. *Int J Cardiol*. 2006; 111(1):142-146.
23. Baykan M, Baykan EC, Turan S, et al. Assessment of left ventricular function and Tei index by tissue Doppler imaging in patients with slow coronary flow. *Echocardiography*. 2009;26(10):1167-1172.
24. Javadi DH, Sotudeh DS, Javadi DA, Rezaee DM, Hajikarimi DM. Echocardiographic evaluation of left and right ventricular function in patients with coronary slow flow syndrome: a comparative study. *Curr Probl Cardiol*. 2022;47(9):100925.
25. Sezgin AT, Topal E, Barutcu I, et al. Impaired left ventricle filling in slow coronary flow phenomenon: an echo-Doppler study. *Angiology*. 2005;56(4): 397-401.
26. Narimani S, Hosseinsabet A, Pourhosseini H. Effect of coronary slow flow on the longitudinal left ventricular function assessed by 2-dimensional speckle-tracking echocardiography. *J Ultrasound Med*. 2016;35(4):723-729.

27. Shui Z, Wang Y, Sun M, et al. The effect of coronary slow flow on left atrial structure and function. *Sci Rep*. 2021;11(1):7511.
28. Nurkalem Z, Gorgulu S, Uslu N, et al. Longitudinal left ventricular systolic function is impaired in patients with coronary slow flow. *Int J Cardiovasc Imaging*. 2009;25(1):25-32.
29. Seyyed Mohammadzad MH, Khademvatani K, Gardeshkhah S, Sedokani A. Echocardiographic and laboratory findings in coronary slow flow phenomenon: cross-sectional study and review. *BMC Cardiovasc Disord*. 2021;21(1):230.
30. Elsherbiny IA. Left ventricular function and exercise capacity in patients with slow coronary flow. *Echocardiography*. 2012;29(2):158-164.
31. Tekin G, Tekin A, Sezgin AT, et al., Association of slow coronary flow phenomenon with abnormal heart rate recovery. *Turk Kardiyol Dern Ars*. 2007;35(5):289-294
32. Askin L. Evaluation of heart rate recovery index in patients with coronary slow flow: preliminary results. *Eur Rev Med Pharmacol Sci*. 2021;25(24): 7941-7946.
33. Chen Y, Yu Y, Zou W, Zhang M, Wang Y, Gu Y. Association between cardiac autonomic nervous dysfunction and the severity of coronary lesions in patients with stable coronary artery disease. *J Int Med Res*. 2018;46(9):3729-3740.
34. Youn HJ, Park CS, Moon KW, et al. Relation between Duke treadmill score and coronary flow reserve using transesophageal Doppler echocardiography in patients with microvascular angina. *Int J Cardiol*. 2005;98(3):403-408.
35. Anjos-Andrade FD, Sousa AC, Barreto-Filho JA, et al. Chronotropic incompetence and coronary artery disease. *Acta Cardiol*. 2010;65(6):631-638.
36. Sarma S, Stoller D, Hendrix J, et al. Mechanisms of chronotropic ıncompetence in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2020;13(3):e006331.
37. Lauer MS, Mehta R, Pashkow FJ, Okin PM, Lee K, Marwick TH. Association of chronotropic incompetence with echocardiographic ischemia and prognosis. *J Am Coll Cardiol*. 1998;32(5):1280-1286.