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The Relationship Between H_2FPEF Score and Coronary Slow Flow Phenomenon

Koroner Yavaş Akım Fenomeni ile H_2FPEF Skoru ile Arasındaki Ilişki

ABSTRACT

Objective: Diastolic dysfunction plays an important role in the pathophysiology of both coronary slow flow phenomenon and heart failure with preserved ejection fraction, which could be predicted by the H_2FPEF score. We sought to investigate the association of H_2FPEF score with coronary slow flow phenomenon in subjects undergoing coronary angiography for suspected stable ischemic heart disease.

Methods: The study included 228 consecutive individuals [60.5% male, mean age 52.6 (10.1)]. Subjects with non-obstructive coronary artery disease were classified as coronary normal flow (n=112) and coronary slow flow (n=116) after confirmation of coronary angiography results. H_2FPEF score of each participant was calculated.

Results: Subjects with coronary slow flow phenomenon were more likely to be male (75% vs. 45.5%, $P < .001$) and have a higher body mass index than that of normal flow group [30.5 (2.9) vs. 29.3 (2.8), $P=.001$]. H_2FPEF score was significantly higher in the former group [2 (2-4) vs. 0 (0-1), $P < .001$]. H_2FPEF score was also positively correlated with mean corrected thrombolysis in myocardial infarction frame count ($r=0.725$, $P < .001$). On multivariate logistic regression analysis, male gender [odds ratio: 4.580, 95% CI: 1.700-12.336, $P=.003$], current smoker [OR: 2.398, 95% CI: 1.064-5.408, $P=.035$], total cholesterol [OR: 1.011, 95% CI: 1.001-1.021, $P=.026$], and H_2FPEF score [OR: 3.111, 95% CI: 2.160-4.480, $P < .001$] were found to be the independent predictors of coronary slow flow phenomenon.

Conclusion: We found that the H_2FPEF score, which is useful in demonstrating diastolic dysfunction, is independently associated with coronary slow flow pattern in suspected ischemic heart disease.

Keywords: Coronary slow flow phenomenon, diastolic dysfunction, H_2FPEF score, TIMI frame count

ÖZET

Amaç: Diyastolik disfonksiyon; koroner yavaş akım ve kalp yetersizliği tanısında kullanılan H_2FPEF skorunun patofizyolojisinde temel rol oynamaktadır. Amacımız; stabil anjinası olan ve koroner anjiyografi uygulanan hastalarda H_2FPEF skoru ve koroner yavaş akım arasındaki ilişkiyi araştırmaktır.

Yöntemler: Çalışmaya 228 hasta alındı [%60,5 erkek, ortalama yaş 52,6 (10,1)]. Uygulanan koroner anjiyografi sonrası ciddi tıkanıklığı olmayan koroner arter hastalığı tanısı alan hastalar, normal koroner akım (n:112) ve koroner yavaş akım (n:116) olmak üzere iki gruba ayrıldı. Bu hastaların H_2FPEF skorları hesaplandı.

Bulgular: Koroner yavaş akım grubunda normal akım grubuna göre erkek oranı (%75'e karşı %45.5, $P < .001$) ve vücut kitle indeksi [30.5 (2.9)'e karşı 29.3 (2.8), $P = .001$] daha fazlaydı. H_2FPEF skoru anlamlı olarak koroner yavaş akım grubunda yüksekti [2 (2-4) vs 0 (0-1), $P < .001$]. Ayrıca, H_2FPEF skoru ile TIMI kare sayısı arasında pozitif korelasyon vardı ($r = 0.725$, $P < .001$). Çok değişkenli lojistik regresyon analizinde, erkek cinsiyet (OO) = 4.580; %95 GA = 1.700-12.336, $P = .003$), sigara kullanımı (OO = 2.398; %95 GA = 1.064-5.408, $P = .035$), total kolesterol (OO = 1.011; %95 GA = 1.001-1.021, $P = .026$) ve H_2FPEF skoru (OO = 3.111; %95 GA = 2.160-4.480, $P < .001$) koroner yavaş akımı öngörmede bağımsız belirteçler olduğu izlendi.

Sonuç: Şüpheli iskemik kalp hastalığında; diyastolik disfonksiyonu tespit etmede kullanılan H_2FPEF skorunun koroner yavaş akım ile bağımsız bir şekilde ilişkili olduğunu bulduk.

Anahtar Kelimeler: Koroner yavaş akım fenomeni, diyastolik disfonksiyon, H_2FPEF skoru, TIMI kare sayısı

Coronary slow flow phenomenon (CSFP) is an angiographic pathology characterized by the slow passage of contrast without obstructive coronary artery disease. The frequency of CSFP has been reported between 1% and 7% in previous studies.[1]

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Although the underlying causes of CSFP are still unknown, its diagnosis and treatment are highly important because of the association with cardiovascular complications including recurrent angina, unnecessary hospitalization and intervention, and fatal arrhythmias, and it may also be an early indicator of atherosclerosis.[2-4] Moreover, various pathophysiological conditions such as microvascular and endothelial dysfunction, small vessel disease, inflammatory diseases, and neurohormonal imbalance are related to this phenomenon.[5] In addition, studies have ascertained the presence of diastolic filling abnormality/diastolic dysfunction in CSFP.[6] Hence, since diastole duration and diastolic filling are the main determinants of coronary blood flow, clinical variables affecting these processes can also change blood flow dynamics.

As is known, diastolic dysfunction, which is associated with mortality, plays a key role in the development of heart failure (HF).[7] Relatedly, left ventricular diastolic dysfunction makes an important contribution to the understanding of HF with preserved ejection fraction (HFpEF).[8] The increasing frequency of HFpEF constituting approximately half of patients with HF, difficulty in diagnosis, as well as lack of effective medical treatment on mortality have made this HF subgroup an increasingly significant clinical entity. Large-scale studies focusing on early diagnosis and treatment in HFpEF may provide new estimations that could have a positive impact on mortality. For this purpose, Reddy et al[9] proposed the H_2FPEF score, which consists of easily accessible clinical and echocardiographic parameters, to help differentiate HFpEF patients from non-cardiac exertional dyspnea. Thus, with this score, we may have had an opportunity to evaluate diastolic dysfunction with a more holistic approach that includes clinical and echocardiographic parameters, rather than demographic or ultrasonographic methods only. Thereby, we might have captured a novel and practically feasible tool to better comprehend the association of left ventricular diastolic dysfunction with coronary blood flow. We sought to investigate the relationship between H_2FPEF score and coronary flow pattern in patients without coronary artery stenosis.

ABBREVIATIONS

AF	Atrial fibrillation
BMI	Body mass index
CA	Coronary angiography
CNF	Coronary normal flow
CSF	Coronary slow flow
CSFP	Coronary slow flow phenomenon
cTFC	Corrected TFC
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
LAD	Left anterior descending
LCx	Left circumflex artery
LDL-C	Low-density lipoprotein cholesterol
mcTFC	Mean corrected TFC
non-STEMI	Non-ST-segment elevation myocardial infarction
RCA	Right coronary artery
ROC	Receiver operating characteristic
RV	Right ventricular
sPAP	Systolic pulmonary artery pressure
STEMI	ST-segment elevation myocardial infarction
TFC	TIMI frame count
TIMI	Thrombolysis in myocardial infarction
TRVmax	Maximal tricuspid regurgitation velocity

Methods

Study Population

This single-center, retrospective, and observational study was composed of a total of 228 consecutive patients aged >18 years who underwent coronary angiography (CA) for suspected stable ischemic heart disease from January 2018 through April 2019. Overall, 3387 patients underwent CA during the enrollment period, 3159 of whom were excluded from the final analysis because of missing echocardiographic or demographic data (n=405) or the presence of at least one of the exclusion criteria (n=2754). Subjects were excluded if they had one of the following conditions: acute coronary syndromes including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (non-STEMI), and unstable angina pectoris, ejection fraction <50%, presence of obstructive coronary artery disease on CA (defined as stenosis of > 40%), significant valvular heart disease (greater than mild stenosis, greater than moderate regurgitation), prior coronary artery bypass graft surgery, coronary ectasia, a myocardial bridge or percutaneous coronary intervention, active infection, chronic inflammatory disease, hepatic and renal disease, known cancer. Patients were divided into 2 groups as coronary normal flow (CNF) and coronary slow flow (CSF) by the joint decision of 2 independent experienced invasive cardiologists who were blinded to the results of the present study. In case of a disagreement, the frames were referred to a third observer. The study was conducted according to the recommendations set forth by the Declaration of Helsinki on biomedical research involving human subjects. Çukurova University School of Medicine Clinical Research Ethics Committee approved the study protocol (ethic protocol number: 2020/104-23, date: October 02, 2020). The need for a written informed consent form from each participant was waived due to the retrospective nature of the study.

Demographic Parameters and Transthoracic Echocardiography

Demographic, clinical, echocardiographic, and laboratory data were obtained from patient medical records using admission numbers that were unique to each patient or by telephone interview if needed. Transthoracic echocardiography was performed by licensed physicians who were unaware of any clinical data of the participants using a Vivid 7 ultrasound cardiovascular system (GE Vingmed Sound, Horten, Norway) with a 2.5-3.5 MHz transducer, with respect to criteria of the American Society of Echocardiography. The following echocardiographic parameters were recorded: ejection fraction (%), left atrium anteroposterior diameter (mm), mitral inflow E and A wave velocity (cm/s), mitral E/A ratio, lateral tissue Doppler E/e' ratio, maximal tricuspid regurgitation velocity (TRV_{max}), and systolic pulmonary artery pressure (sPAP) (mm Hg). Left ventricular ejection fraction was calculated using the biplane Simpson's method. Blood counts were measured by a Sysmex K-1000 (Block Scientific, Bohemia, NY, USA) autoanalyzer within 5 minutes of sampling. Plasma triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), glucose, uric acid, and creatinine concentrations were measured with an automated chemistry analyzer (Abbott Aeroset, Minnesota, USA)

using commercial kits (Abbott). Glomerular filtration rate was calculated using The Chronic Kidney Disease Epidemiology Collaboration equation. Hypertension was defined as a recorded blood pressure of >140/90 mm Hg or current use of any antihypertensive drugs. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL, a random plasma glucose concentration of ≥200 mg/dL, or use of oral hypoglycemic agents or insulin. Dyslipidemia was defined as LDL-C >130 mg/dL or total cholesterol >200 mg/dL or taking medications for dyslipidemia. Atrial fibrillation (AF) was determined from clinical history and an electrocardiogram. Current smoker was described as the presence of smoking status based on admission records.

Coronary Angiography and Thrombolysis in Myocardial Infarction Frame Count

Subjects were selected consecutively from those with stable angina and documented coronary ischemia on an exercise stress test or myocardial perfusion imaging during the study period. Coronary angiography was performed via a femoral approach using the standard Judkins technique for all subjects of the study by experienced interventional cardiologists. During CA, iohexol (350/200 mL, Gebze, Kocaeli, Turkey) was injected as a contrast agent. All images were collected at a frame rate of 30 frames/s. Coronary arteries were visualized in the left and right oblique plans, and cranial and caudal angles. All of the study patients had normal or near-normal coronary arteries, defined as stenosis of 40% or less. Coronary flow velocity was evaluated by the thrombolysis in myocardial infarction (TIMI) frame count (TFC) method as defined by Gibson et al.[10] The CSFP was defined as a TFC greater than 27/frame in at least 1 epicardial coronary artery. Thrombolysis in myocardial infarction frame count was measured for each coronary vessel. Corrected TFC (cTFC) was measured for the left anterior descending (LAD) coronary artery and divided by 1.7 to correct for its longer length (LAD-cTFC).[10] Mean corrected TFC (mcTFC) for all individuals was calculated by dividing the sum of TFC values of corrected LAD, left circumflex artery (LCx), and right coronary artery (RCA) by 3.

H_2FPEF Score

We calculated the H_2FPEF score, which has a value between 0 and 9, from the following 6 weighted items related to each patient's background: body mass index (BMI) >30 kg/m^2, ≥2 antihypertensive medicines, paroxysmal or persistent AF, age >60 years, and Doppler echocardiography data at rest (sPAP >35 mm Hg, tissue doppler E/e' >9). Points were assigned to these 6 variables as follows: AF, 3 points; BMI, 2 points; others, 1 point, as previously described.[9] The H_2FPEF score was the sum of these points. Body mass index is calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Reproducibility

Intra- and inter-observer agreement for LAD-cTFC, LCx-TFC, and RCA-TFC were evaluated in 20 randomly selected participants. The intraclass correlation coefficients for interobserver agreement of LAD-cTFC, LCx-TFC, and RCA-TFC were 0.89 [(95% CI, 0.73-0.96), $P < .001$], 0.86 [(95% CI, 0.67-0.95), $P < .001$], and [0.85 (95% CI, 0.62-0.94), $P < .001$], while the intraobserver agreements were 0.95 [(95% CI, 0.88–0.98), $P < .001$], 0.94 [(95% CI, 0.85-0.98), $P < .001$], and 0.94 [(95% CI, 0.85-0.98), $P < .001$], respectively.

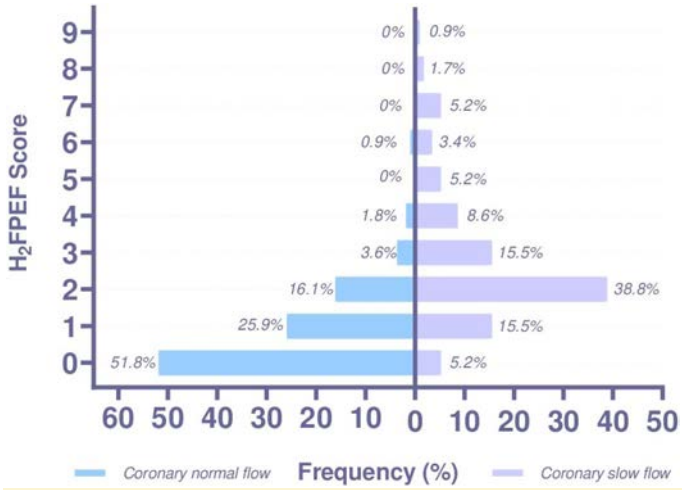

Figure 1. Distribution of H_2FPEF score between the groups by coronary flow pattern.

Statistical Analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences Statistics for Windows, v.20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean (standard deviation) or median (interquartile ranges, 25th-75th percentiles), whereas categorical variables are expressed as percentage (%) and number (n). Continuous variables were tested for normality distribution using an analytical method (Kolmogorov–Smirnov test) and visual methods (histograms and probability plots). The independent sample *t*-test or Mann–Whitney *U* test was used to analyze continuous variables as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test. Spearman's correlation analysis was used to investigate the association of H_2FPEF score with mcTFC. Multivariate logistic regression analysis was used to identify independent predictors of CSFP. All significant parameters with a *P* value of ≤.25 in the univariate analysis were selected for the multivariate model. Components of the H_2FPEF score were not included in the regression analysis due to the internal correlation with the score. Intra- and interobserver agreements were evaluated with intraclass correlation coefficients by one-way random and two-way mixed models, respectively. Sensitivity, specificity, positive, and negative predictive values of the scores, and the optimal cut-off point for determining CSFP were calculated using receiver operating characteristic (ROC) curve analysis. The area under the curve value was calculated as a measure of the accuracy of the test. Youden index was utilized to determine the predictive value of the H_2FPEF score. A two-tailed *P* value of less than .05 was considered statistically significant.

Results

Laboratory and Demographic Characteristics

The mean age of the study population is 52.6 (10.1) years, 60.5% of whom are male. There was no difference in terms of age between the groups. Subjects with CSFP were more likely to be male (75% vs. 45.5%, $P < .001$) and have a higher BMI [30.5 (2.9) vs. 29.3 (2.8), $P = .001$]. The proportions of smoking and AF were more frequent in the CSF group than in the normal

Table 1. Demographic and Laboratory Characteristics of the Study Population

	Slow Flow (n=116)	Normal Flow (n=112)	All (n=228)	*P*
Demographic parameters				
Age (years)	53.2 (10.1)	52.0 (10.2)	52.6 (10.1)	.360
Gender, male (n, %)	87 (75)	51 (45.5)	1138 (60.5)	<.001
Body mass index (kg/m^2)	30.5 (2.9)	29.3 (2.4)	29.9 (2.8)	.001
Diabetes mellitus (n, %)	34 (29.3)	25 (22.3)	59 (25.9)	.230
Hypertension (n, %)	48 (41.4)	36 (32.1)	84 (36.8)	.150
Current smoker (n, %)	53 (45.7)	31 (27.7)	84 (36.8)	.005
Atrial fibrillation (n, %)	18 (15.5)	2 (1.8)	20 (8.8)	<.001
Laboratory findings				
Glucose (mg/dL)	100 (88-133)	94 (82-114)	96 (84-122)	.290
CRP (mg/dL)	3.3 (1.9-5.5)	3.1 (2.2-5.9)	3.2 (2.1-5.7)	.730
Triglycerides (mg/dL)	215 (141-269)	168 (114-224)	186 (124-245)	.023
HDL-C (mg/dL)	43.8 (11.5)	43.5 (10.2)	43.6 (10.8)	.840
LDL-C (mg/dL)	135.6 (32.7)	125.9 (33.0)	131.1 (33.1)	.046
Total cholesterol (mg/dL)	206.1(42.6)	190.5 (44.2)	198.4 (43.9)	.007
e-GFR (mL/min/1.73 m^2)	101.8 (16.7)	102.0 (15.4)	101.9 (16.1)	.950
Urea (mg/dL)	27.6 (23.9-33.0)	26.0 (21.0-35.0)	27.0 (22.6-33.7)	.130
Hemoglobin (mg/dL)	14.3 (1.4)	13.1 (1.6)	13.7 (1.6)	<.001
Systolic blood pressure (mm Hg)	124.9 (9.6)	123.6 (11.7)	124.3 (10.7)	.400
Diastolic blood pressure (mm Hg)	79.6 (7.7)	78.7 (10.7)	79.3 (9.3)	.340
Heart rate (bpm)	74.9 (7.0)	76.2 (8.4)	75.5 (7.8)	.190
H_2FPEF score	2 (2-4)	0 (0-1)	1 (0-2)	<.001
Medications taken before coronary angiography, n (%)				
ACE inhibitors	30 (25.9)	17 (15.2)	47 (20.6)	.046
ARB	15 (12.9)	8 (7.1)	23 (10.1)	.147
Calcium channel blockers	20 (17.2)	12 (10.7)	32 (14.0)	.156
Beta-blockers	30 (25.9)	18 (16.1)	48 (21.1)	.070
Diuretics	40 (34.5)	14 (12.5)	54 (23.7)	<.001
Statins	11 (9.5)	3 (2.7)	14 (6.1)	.032
Acetylsalicylic acid	26 (22.4)	17 (15.2)	43 (18.9)	.163
Oral anticoagulants	12 (10.3)	2 (1.8)	14 (6.1)	.007

Data are presented as numbers and percentages (%), mean (standard deviation) or median (interquartile range). *P* value was calculated using the independent samples *t*-test or the Mann–Whitney *U*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables as appropriate. *P* value < .05 was considered significant.
CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; e-GFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers.

flow group (*P*=.005 and *P* < .001, respectively). Total cholesterol, LDL-C, and hemoglobin levels were statistically higher in the former. The current use of angiotensin-converting enzyme inhibitors, diuretics, and oral anticoagulants was more common in patients with CSF. H_2FPEF score was also significantly higher in the CSF patients than in the CNF patients [2 (2-4) vs. 0 (0-1), *P* < .001]. Approximately half of the subjects (51.8%) with CNF had an H_2FPEF score of 0, while the most common H_2FPEF score was 2 among CSF patients (33.8%) (Figure 1). Demographic parameters, laboratory findings, and medical treatments of the study population are listed in Table 1.

Echocardiographic and Angiographic Assessment

As shown in Table 2, patients with CSF had lower mitral inflow E wave velocity and mitral E/A ratio (*P*=.01 and *P*=.004, respectively), whereas tissue Doppler E/e' ratio and sPAP were higher (*P* < .001, for both). Coronary slow flow individuals had wider left atrium diameter (*P*=.020). About 78.4% of the low-score group, those with H_2FPEF score of 0-1, were CNF; on

Table 2. Echocardiographic and Angiographic Findings

	Slow Flow (n=116)	Normal Flow (n=112)	All (n=228)	*P*
Ejection fraction (%)	59.5 (5.1)	60.7 (4.9)	59.8 (5.0)	.270
LA diameter (mm)	38.6 (4.9)	35.0 (5.1)	37.9 (5.1)	.020
Mitral inflow E wave velocity (cm/s)	82.5 (12.6)	86.4 (9.9)	84.4 (11.5)	.010
Mitral inflow A wave velocity (cm/s)	56.6 (8.4)	54.5 (8.1)	55.5 (8.3)	.059
Mitral E/A ratio	1.49 (0.3)	1.62 (0.3)	1.56 (0.3)	.004
Tissue Doppler E/e' ratio	9.1 (2.5)	6.4 (1.9)	8.3 (2.3)	<.001
TRV_{max}	2.3 (0.4)	2.0 (0.4)	2.2 (0.5)	.001
sPAP (mm Hg)	24.1 (8.4)	18.2 (4.3)	21.2 (7.3)	<.001
TIMI frame count (TFC)				
LAD	51.7 (5.2)	31.3 (5.0)	41.7 (11.4)	<.001
Corrected LAD	30.3 (3.4)	18.4 (2.9)	24.5 (6.7)	<.001
LCx	31.2 (4.2)	21.3 (4.7)	26.3 (6.7)	<.001
RCA	32.1 (4.9)	22.0 (4.2)	27.1 (6.8)	<.001
mcTFC	26.9 (4.1)	15.4 (1.5)	21.3 (6.6)	<.001

Data are presented as numbers and percentages (%) or mean (standard deviation). *P* value was calculated using the independent samples *t*-test for continuous variables. *P* value < .05 was considered significant.
LA, left atrium; TRV_{max}, maximal tricuspid regurgitation velocity; sPAP, systolic pulmonary artery pressure; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery; mcTFC, mean corrected thrombolysis in myocardial infarction (TIMI) frame count.

the contrary, 78.6% of the high-score subjects, those with ≥2 H_2FPEF score, had at least 1-vessel CSF (Figure 2). There was no relationship between the number of the involved vessel and conventional risk factors, except for the proportion of AF, which is more common in subjects with CSF who have at least 2-vessel involvement (Table S1).

Correlates of Coronary Slow Flow Phenomenon

On multivariate logistic regression analysis, male gender [odds ratio (OR): 4.580, 95% CI: 1.700-12.336, *P*=.003], current smoker [OR: 2.398, 95% CI: 1.064-5.408, *P*=.035], total cholesterol [OR: 1.011, 95% CI: 1.001-1.021, *P*=.026], and H_2FPEF score [OR: 3.111, 95% CI: 2.160-4.480, *P* < .001] were found to be the independent predictors of CSFP (Table 3). H_2FPEF score was positively correlated with mcTFC (r=0.725, *P* < .001) (Figure 3). In ROC curve analysis, an H_2FPEF score of ≥2 was determined as the most appropriate point to predict CSFP with 79% sensitivity and 77% specificity, based on the Youden index (Figure 4). The diagnostic accuracy of the score is 0.842 (95% CI: 0.791-0.894, *P* < .001) by the area under the curve of ROC.

Discussion

We have evaluated the relationship of CSFP to H_2FPEF score in patients who underwent CA for suspected stable ischemic heart disease. The main finding of the present study is that the H_2FPEF score, which is used to predict diastolic dysfunction, is also a determinant of CSFP. To the best of our knowledge, this is the first study to investigate the association of H_2FPEF score with CSF.

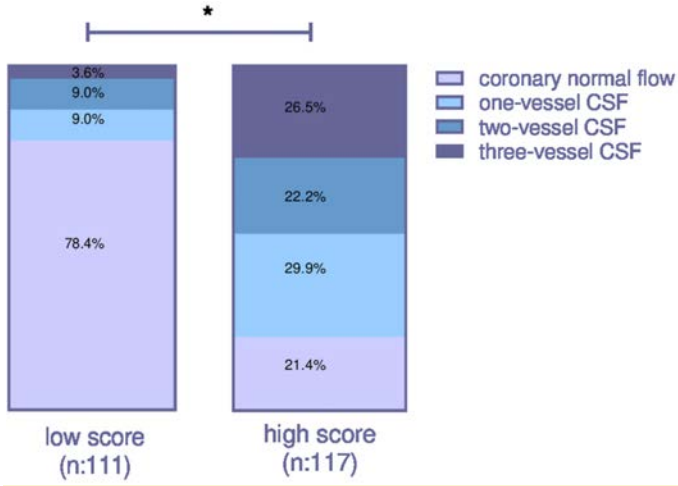

Figure 2. Slow flow pattern (number of involved vessels) in the study population. *Chi square *P* < .001. Those with H_2FPEF score of 0-1 were defined as the low score group, and those with ≥2 were defined as the high score group with respect to receiver operating characteristic curve analysis. CSF, coronary slow flow.

It is well-established that blood flow to the heart occurs mainly during diastole.[11] Diastolic filling abnormality and diastolic dysfunction are associated with CSF. Moreover, impaired diastolic parameters may also influence coronary blood flow through increased extravascular resistance and decreased maximal coronary filling time.[12,13] We hypothesized that 2 clinical entities associated with diastolic dysfunction, CSFP and H_2FPEF score,

Table 3. Multivariate Regression Analysis Associated with Independent Determinants of Coronary Slow Flow Phenomenon

Variable	Adjusted OR (95% CI)	*P*
Gender, male, n (%)	4.580 (1.700-12.336)	.003
Diabetes mellitus, n (%)	0.699 (0.262-1.862)	.470
Current smoker, n (%)	2.398 (1.064-5.408)	.035
Hemoglobin (mg/dL)	1.307 (0.962-1.776)	.086
Total cholesterol (mg/dL)	1.011 (1.001-1.021)	.026
Triglycerides (mg/dL)	1.000 (0.997-1.002)	.770
H_2FPEF score	3.111 (2.160-4.480)	<.001
ACE inhibitors, n (%)	1.511 (0.508-4.488)	.460
Diuretics, n (%)	0.518 (0.194-1.383)	.190
Statins, n (%)	1.774 (0.207-15.204)	.600
Oral anticoagulants, n (%)	0.412 (0.056-3.036)	.380

Nagelkerke R^2=0.592; −2 Log likelihood, 182.116; model chi-square: 133.889.
ACE, angiotensin-converting enzyme.

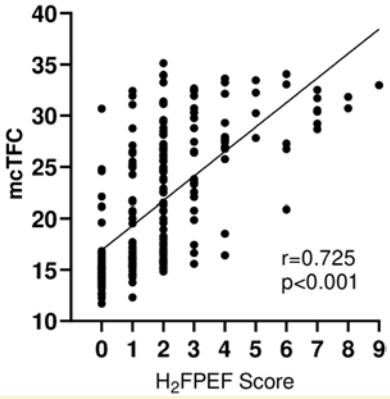

Figure 3. Correlation between mcTFC and H_2FPEF score. mcTFC, mean corrected thrombolysis in myocardial infarction (TIMI) frame count.

may be interrelated. Parallel with this assumption, we then found that the H_2FPEF score was an independent predictor of CSF in comparison with CNF. Coronary slow flow phenomenon, which is related to many cardiac symptoms (i.e., chest pain, dyspnea), could increase morbidity and mortality by leading to unnecessary hospitalization and CA procedure. For instance, in a study by Cakmak et al,[14] CSFP was reported to be a marker of sudden cardiac death. Therefore, even though the etiology of CSFP is still unclear, early diagnosis and treatment are crucial. To close this gap in the existing literature, Sezgin et al[6] reported higher peak late diastolic filling rate, lower early-late rate ratio (E/A ratio), longer left ventricular isovolumetric relaxation, mitral deceleration, and mitral ejection time, all of which are

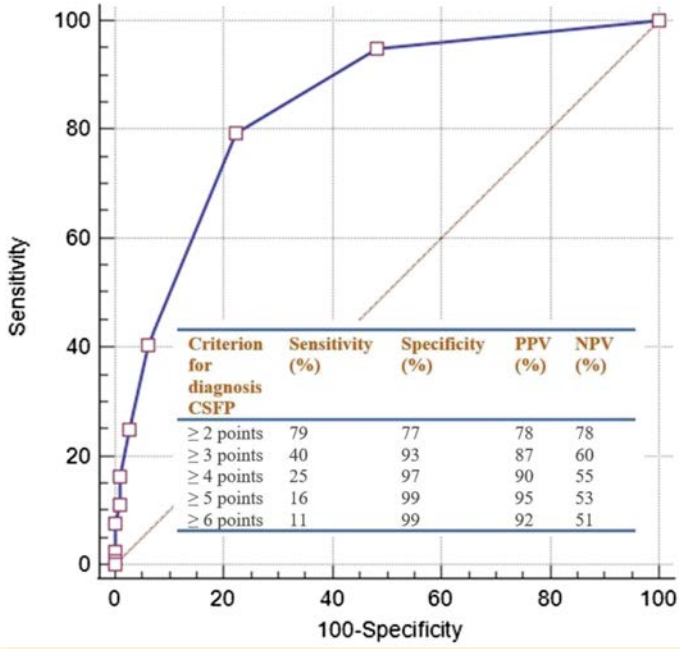

Figure 4. Receiver operator characteristic curve analysis of H_2FPEF score for determining predicting coronary slow flow phenomenon in subjects undergoing suspected stable ischemic heart disease. CSFP, coronary slow flow phenomenon; PPV, positive predictive value; NPV, negative predictive value.

echocardiographic indices of diastolic dysfunction, in patients with CSFP compared to CNF patients. In parallel with these findings, we also determined lower mitral E-wave velocity and E/A ratio, higher E/e' ratio in CSF patients, compared to the control group with CNF. Using the H_2FPEF score instead of searching for certain echocardiographic or clinical parameters alone may have enabled us to obtain a more consistent, integrative, and easy-to-apply approach in disclosing the relationship between diastolic dysfunction and CSFP. Given the large number of studies revealing the main effect of diastolic dysfunction on HFpEF, we considered it is important to address whether this score is associated with diastolic dysfunction in the etiopathogenesis of CSFP and then showed in our study that a cut-off of ≥2 predicts CSFP. Hereby, we can speculate that we have demonstrated the linkage between diastolic dysfunction and CSFP, with a clinically multifactorial variable, H_2FPEF score.

When examining the relationship between the parameters that make up the H_2FPEF score and CSF in-depth, we notice that all the parameters are well-correlated with CSFP. For instance, Luo et al[15] found that TFC was significantly higher for each coronary artery in patients with AF compared to the control group. In addition, this prolongation in TFC was found to be more pronounced in longer-lasting AF episodes such as permanent or long-standing AF. In support of this, a deterioration in left atrial global longitudinal strain, a determinant of AF, was also detected in CSF.[16] It should be noted that several publications regarding a strong and positive association of CSFP with BMI are available.[17,18] The above-mentioned relationship may be partially explained by the fact that both clinics, obesity and CSF, are associated with common pathophysiological conditions including impaired fasting glucose, insulin resistance, endothelial dysfunction, and atherosclerosis. Considering the strong relationship between hypertension and coronary artery disease, it is not surprising that CSF, which is considered one of the indicators of early atherosclerosis, is more common in hypertensive patients.[19] In patients with CSF, impaired right ventricular (RV) diastolic dysfunction,[20] free wall, septal wall, and RV global longitudinal strain[21,22] might exhibit its indirect relationship with pulmonary hypertension. Besides, in measurements made with magnetic resonance flow quantification, decreased peak systolic and mean flow were detected in those with pulmonary hypertension compared to the healthy control group, and systolic-to-diastolic flow ratio was also shown inversely related to RV pressure and mean flow per RV mass, all of which demonstrate the link between CSFP and pulmonary hypertension.[23] Finally, reports have delineated the relationship of advanced age with increased TFC in both AF patients and healthy individuals.[15]

The H_2FPEF score is also associated with increased mortality and re-hospitalization in HFpEF.[24] Additionally, the low score group, defined as 0-1 points in the former study, was similar to the score of patients with the CNF in our study. In the report of Suzuki et al,[25] the H_2FPEF score was used to predict chronic HF-related events (cardiovascular death and re-hospitalization due to decompensated HF) in stable outpatients with at least 1 cardiovascular risk factor. The H_2FPEF score was also investigated in a study of non-STEMI patients without HF and was found to be correlated with the SYNTAX score, an indicator of the severity of coronary artery disease, and 30-day major adverse cardiovascular

events.[26] Besides, similar to ours, this study reported that a cut-off value of >2 predicted the high SYNTAX score and indicated that the H_2FPEF score may have both prognostic and diagnostic value not only in HF patients but also in other groups of patients. Likewise, CSFP has been associated with diffuse atherosclerosis, a predictor of poor outcomes. This analogy might also explain the relationship with the score from a prognostic point of view. Namely, when all these intersections are taken together, we may state that the H_2FPEF score is quite useful in clarifying the relationship between slow flow and diastolic dysfunction. The presence of a strong positive correlation between the mcTFC and H_2FPEF score and a higher number of the involved vessels for CSF in patients with a score ≥2 also strengthen this unifying implication (Figures 2 and 3).

Limitations

The study has several notable limitations. Although the methodological frontiers are made as clear as possible, the retrospective nature of the study inevitably creates some degree of selection and recall bias. Also, obtaining the results from only a tertiary referral center weakened the generalizability. The diagnosis of normal or near-normal epicardial coronary arteries was made visually rather than using more sensitive and specific methods such as intravascular ultrasonography. Thus, this shortcoming may cause a margin of error in the analysis due to the inappropriate assignment of individuals to the groups. As the study was retrospective, manual injection of contrast agents was operator-dependent and therefore not standardized. All these factors may have caused some participants to be misdiagnosed as CSF due to the slow rate of injection. Since we did not have long-term follow-up data, the relationship between H_2FPEF score and outcome could not be evaluated among CSF patients. Another important limitation is the absence of clinically relevant parameters such as left ventricular mass index or left ventricular end-diastolic pressure that could more clearly reveal the correlation between diastolic dysfunction and CSFP. Finally, probably most importantly, which components of the score contributed, and the extent of the contribution, to the relationship with CSF could not be resolved owing to the insufficient statistical power of our study. Large-scale, prospective, randomized controlled trials are, thus, required.

Conclusion

In the present study, we showed that the H_2FPEF score, which is a simple, cheap, easy-to-use, and non-invasive method, is independently associated with the CSFP. Patients with high scores should, therefore, be followed closely during CA for the development of CSF, which leads to poor outcomes.

Ethics Committee Approval: Ethics committee approval was received from the Çukurova University School of Medicine Clinical Research Ethics Committee (Approval Date: October 2, 2020; Approval Number: 2020/104-23).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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References

1. Wang X, Nie SP. The coronary slow flow phenomenon: characteristics, mechanisms and implications. *Cardiovasc Diagn Ther*. 2011;1(1):37-43. [CrossRef]
2. Wozakowska-Kapłon B, Niedziela J, Krzyzak P, Stec S. Clinical manifestations of slow coronary flow from acute coronary syndrome to serious arrhythmias. *Cardiol J*. 2009;16(5):462-468.
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. [CrossRef]
4. Cin VG, Pekdemir H, Camsar A, et al. Diffuse intimal thickening of coronary arteries in slow coronary flow. *Jpn Heart J*. 2003;44(6):907-919. [CrossRef]
5. Beltrame JF, Limaye SB, Wuttke RD, Horowitz JD. Coronary hemodynamic and metabolic studies of the coronary slow flow phenomenon. *Am Heart J*. 2003;146(1):84-90. [CrossRef]
6. 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. [CrossRef]
7. Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA*. 2011;306(8):856-863. [CrossRef]
8. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2014;11:507-515.
9. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018;138(9):861-870. [CrossRef]
10. 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. [CrossRef]
11. Rovai D, L'Abbate A, Lombardi M, et al. Nonuniformity of the transmural distribution of coronary blood flow during the cardiac cycle. In vivo documentation by contrast echocardiography. *Circulation*. 1989;79(1):179-187. [CrossRef]
12. Galderisi M, Cicala S, Caso P, et al. Coronary flow reserve and myocardial diastolic dysfunction in arterial hypertension. *Am J Cardiol*. 2002;90(8):860-864. [CrossRef]
13. Vogt M, Motz W, Strauer BE. Coronary hemodynamics in hypertensive heart disease. *Eur Heart J*. 1992;13(suppl D):44-49. [CrossRef]
14. Cakmak HA, Aslan S, Gul M, et al. Assessment of the relationship between a narrow fragmented QRS complex and coronary slow flow. *Cardiol J*. 2015;22(4):428-436. [CrossRef]
15. Luo C, Wu X, Huang Z, et al. Documentation of impaired coronary blood flow by TIMI frame count method in patients with atrial fibrillation. *Int J Cardiol*. 2013;167(4):1176-1180. [CrossRef]
16. 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. [CrossRef]
17. 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. [CrossRef]
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. [CrossRef]
19. Sanati H, Kiani R, Shakerian F, et al. Coronary slow flow phenomenon clinical findings and predictors. *Res Cardiovasc Med*. 2016;5(1):e30296. [CrossRef]
20. Yilmaz M, Özlük FÖA, Peker T, Bekler A, Karaağaç K. Right ventricular function and its relation with TIMI frame count in the coronary slow flow phenomenon. *Turk J Med Sci*. 2013;43(1):46-51.

21. Xing Y, Shi J, Yan Y, et al. Subclinical myocardial dysfunction in coronary slow flow phenomenon: identification by speckle tracking echocardiography. *Microcirculation*. 2019;26(1):e12509. [CrossRef]
22. Kemaloğlu Öz T, Eren M, Atasoy I, Gürol T, Soylu Ö, Dağdeviren B. Are biventricular systolic functions impaired in patient with coronary slow flow? A prospective study with three dimensional speckle tracking. *Int J Cardiovasc Imaging*. 2017;33(5):675-681. [CrossRef]
23. Van Wolferen SA, Marcus JT, Westerhof N, et al. Right coronary artery flow impairment in patients with pulmonary hypertension. *Eur Heart J*. 2008;29(1):120-127. [CrossRef]
24. Sun Y, Wang N, Li X, et al. Predictive value of H2FPEF score in patients with heart failure with preserved ejection fraction. *ESC Heart Fail*. 2021;8(2):1244-1252. [CrossRef]
25. Suzuki S, Kaikita K, Yamamoto E, et al. H2 FPEF score for predicting future heart failure in stable outpatients with cardiovascular risk factors. *ESC Heart Fail*. 2020;7(1):65-74. [CrossRef]
26. Bayam E, Kalçık M, Öztürkeri B, et al. The relationship between H2FPEF and SYNTAX scores in patients with non-ST elevation myocardial infarction. *Acta Cardiol*. 2021;76(8):870-877. [CrossRef]

Table S1. Conventional Risk Factors and Medications of Study Population According to Vessel Involvement

	Subjects with At Least 2-Vessel Involvement (n = 71)	Subjects with 1-Vessel Involvement (n = 45)	*P*
Risk factors, n (%)			
Gender (male)	53 (74.6)	34 (75.6)	.910
Diabetes mellitus	22 (31.0)	12 (26.7)	.620
Hypertension	34 (47.9)	14 (31.1)	.074
Current smoker	32 (45.1)	21 (46.7)	.870
Atrial fibrillation	18 (25.4)	0 (0)	<.001
Medications, n (%)			
ACE inhibitors	17 (23.9)	13 (28.9)	.550
ARB	13 (18.3)	2 (4.4)	.030
Calcium channel blockers	14 (19.7)	6 (13.3)	.380
Beta-blockers	20 (28.2)	10 (22.2)	.480
Diuretics	27 (38.0)	13 (28.9)	.310
Acetylsalicylic acid	18 (25.4)	8 (17.8)	.340
Oral anticoagulants	7 (9.9)	5 (11.1)	.530

Data are presented as numbers and percentages (%). *P* value was calculated using the chi-square test or Fisher's exact test for categorical variables as appropriate.
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers.