Acta Cardiol Sin 2021;37:473–483
Original Article
doi: 10.6515/ACS.202109_37(5).20210319A

Coronary Artery Disease

Growth Differentiation Factor 15 is Related with Left Ventricular Recovery in Patients with ST-Elevation Myocardial Infarction after Successful Reperfusion by Primary Percutaneous Intervention

Mustafa Umut Somuncu,[1] Fatih Pasa Tatar,[1] Belma Kalayci,[1] Ahmet Avci,[1] Naile Eris Gudul,[1] Begum Uygur,[2] Ali Riza Demir[2] and Murat Can[3]

Background: The determinants of left ventricular (LV) recovery after successful revascularization in ST-elevation myocardial infarction (STEMI) patients are not clear. In addition, the relationship between growth differentiation factor15 (GDF-15) and left ventricular ejection fraction (LVEF) improvement is also unknown. This study hypothesizes that a low GDF-15 level would be associated with LVEF recovery.

Methods: One hundred and sixty-one STEMI patients were included in this study. Echocardiographic examinations were performed before and 12-18 weeks after discharge. The patients were divided into three groups according to the changes in LVEF as 62 patients with ≥ 10% change, 47 patients with 1-9% change, and 52 patients ≤ 0% change. LV recovery was defined as ≥ 10% LVEF improvement and the predictors of LV recovery were investigated. Moreover, two groups were created according to GDF-15 values, and the follow-up/baseline echocardiographic parameters were compared between these groups.

Results: LV recovery was detected in 38.5% of the patients. Low baseline LVEF [odds ratio (OR): 0.85, 95% confidence interval (CI) 0.82-0.94, p = 0.001], low GDF-15 (OR: 0.79, 95% CI 0.68-0.93, p = 0.004), previous angina (OR: 2.34, 95% CI 1.10-4.96, p = 0.027), and symptom-to-balloon time (OR: 0.97, 95% CI 0.95-1.00, p = 0.043) were independent predictors of LV recovery. The ratios of follow-up/baseline LV end-diastolic volume index, LV end-systolic volume index and wall motion score index were lower in the low GDF-15 group (0.96 vs. 1.04, p < 0.001; 0.96 vs. 1.10, p < 0.001; 0.89 vs. 0.96, p < 0.001). Moreover, being in the low GDF-15 group was associated with LV recovery (OR: 2.93, 95% CI 1.43-6.02, p = 0.001).

Conclusions: Lower GDF-15 level was associated with better LV improvement and less adverse remodeling in STEMI patients.

Key Words: Cardiac remodeling • Left ventricular function • Myocardial infarction • Percutaneous coronary revascularization

INTRODUCTION

Providing mechanical or pharmacological reperfusion decreases mortality rates in the early period after myocardial infarction (MI) in ST-elevation myocardial infarction (STEMI) patients.[1] It has been shown that infarct areas are reduced and left ventricular ejection fraction (LVEF) is partially preserved in patients undergoing a primary percutaneous coronary intervention (PCI).[2,3] How-

Received: October 27, 2020 Accepted: March 19, 2021
[1]Department of Cardiology, Zonguldak Bulent Ecevit University Faculty of Medicine, Zounguldak; [2]Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center, Training and Research Hospital, Istanbul; [3]Department of Biochemistry, Zonguldak Bulent Ecevit University Faculty of Medicine, Zounguldak, Turkey.
Corresponding author: Dr. Mustafa Umut Somuncu, Bülent Ecevit Universitesi Tıp Fakultesi Dekanlıgı Ibn-i Sina Kampusu 67600 Esenköy, Kozlu, Zonguldak, Turkey. Tel: +90 532 340 1525; Fax: +90 372 261 0264; E-mail: usomuncu@gmail.com

ever, despite these interventions, an important amount of myocardial necrosis occurs in a significant number of patients who present with heart failure (HF) with progressive left ventricular (LV) dilatation and diminished LVEF as a result of adverse remodeling.[4,5]

In the months following MI, changes in LV function differ and it is not possible to predict totally in which direction these changes will occur. Long-term worsening of LV function may occur due to inflammation, fibrosis, and myocyte necrosis as well as short-term improvements due to hibernation or stunning.[6,7] Although clinical and angiographic features have been developed for this purpose,[8] determining different predictors can help clinicians to draw a road map.

Growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor-b cytokine superfamily and is also known as macrophage inhibitory cytokine 1 (MIC-1) or nonsteroidal anti-inflammatory drug-activated gene (NAG-1). GDF-15 is released in response to stress.[9] It is synthesized from cardiac tissues in cases of myocardial ischemia or reperfusion and hemodynamic stress.[10]

GDF-15 has an additional prognostic contribution to other known clinical and biochemical markers in STEMI patients.[11,12] Moreover, the prognostic value of GDF-15 has been demonstrated in very long-term studies.[13] However, no previous study has investigated the relationship between LV recovery and GDF-15 in post-MI patients who were successfully revascularized. Therefore, the aim of this study was to determine the relationship between changes in cardiac functions over time in post-MI patients and GDF-15. We also aimed to determine the effects of other clinical, laboratory, and angiographic features on changes in LV echocardiographic parameters.

METHODS

Study population

The study population consisted of patients who presented to our center with STEMI and underwent revascularization with primary PCI. The exclusion criteria were patients: 1) who died during angiography or hospital follow-up; 2) with an active infection, malignancy or active rheumatic disease that could trigger inflammation; 3) who had a cardiac arrest during hospitalization; 4) who were admitted 12 hours after the onset of symptoms; 5) with planned coronary artery bypass graft (CABG) surgery after angiography; and 6) who did not come to their control visits or echocardiographic examinations after 12-18 weeks. In addition, patients who were hospitalized and underwent coronary procedures due to acute coronary syndrome before control echocardiography were also excluded. As LV recovery is not expected in patients in whom successful coronary revascularization cannot be achieved, patients with thrombolysis in myocardial infarction (TIMI) flow 0-1 after primary percutaneous coronary procedure were also excluded from the study. Furthermore, patients with baseline LVEF > 50% were also excluded because there was little expectation of LVEF improvement. Consequently, a total of 161 patients were included as the study population.

Electrocardiography (ECG) findings of each patient were analyzed to determine the type of MI immediately after admission to the emergency department. ST-segment resolution after the procedure was again evaluated by ECG. The lead with the maximum resolution was chosen for the evaluation, and the resolution was categorized as complete (≥ 70%), partial (30% to 70%) and no (< 30%) resolution. All PCI procedures were performed by operators performing more than 100 PCIs per year in a single center.

After loading antiplatelets and heparin during the procedure, dual antiplatelet maintenance treatment was given after the procedure. High doses of statins were administered as soon as possible. Beta-blockers and renin-angiotensin system (RAS) inhibitors were started within 24 hours if tolerated, and we tried to achieve the maximum dose in a controlled manner. Informed consent forms were obtained from all patients and approval was obtained from the local ethics committee. The study was designed in accordance with the Helsinki Declaration.

Analysis of patient data

The patients' demographic information, medical charts, and laboratory parameters were recorded. Venous blood samples were obtained by venipuncture for biochemical parameters. GDF-15 has been reported to increase in the first few hours and then reach a peak value in 12-24 hours in STEMI patients, and measuring GDF-15 in the first 24 hours has been reported to provide useful information for the short and long term.[14]

For this reason, blood samples for GDF-15 were collected between 12-24 hours after hospital admission. All of our patients underwent a primary PCI intervention immediately after hospital admission. Therefore, blood samples for GDF-15 were taken after the procedure. All samples were placed in EDTA-coated vacuum tubes. Immediately thereafter, the samples were separated by centrifugation and then stored at -70 °C. Serum GDF-15 levels were measured using an enzyme-linked immunosorbent assay (ELISA) method with a commercial ELISA kit (USCN Life, Wuhan Eiaab Science Co. Ltd, Optics Valley, Wuhan, China), according to the manufacturer's instructions. This particular immunoassay utilized the quantitative technique of sandwich ELISA. GDF-15 tests were accomplished with an Elx800 automatic ELISA reader (BioTek, Winooski, VT, USA) and the results were calculated from the calibration curve. The sensitivity of the GDF-15 assay was < 0.063 ng/mL, and the detection range was 0.156-10 ng/ml. The coefficients of intraassay and interassay variation of GDF-15 were < 10%-< 12%.

Echocardiographic analysis

All patients underwent detailed echocardiographic examination within the first 24-72 hours after PCI and 12-18 weeks (mean 14 weeks) after discharge. LVEF was calculated by the Simpson method with a transthoracic echocardiography device (Vivid S5 probe 3 S-RS, GE Healthcare, Wisconsin, USA). LV diameters were measured using M-mode as recommended by the American Society of Echocardiography.[12] Ventricular dilatation was obtained using the left ventricular end-diastolic volume index (LVEDVI) and left ventricular end-systolic volume index (LVESVI). LVEDVI and LVESVI were calculated by dividing the LV end-diastolic and end-systolic volumes measured by the Simpson method, to the body surface area. Posterior wall thickness was measured to determine LV hypertrophy. To evaluate regional systolic function, the left ventricle was divided into a 16-segment model as recommended by American Society of Echocardiography.[15] For each segment, wall motion was scored from 1 (normal) to 4 (dyskinetic) and the obtained score was divided by 16 to calculate the wall motion score index (WMSI). LV remodeling was determined by LVEDVI and LVESVI ratios obtained by dividing follow-up volume indexes to baseline volume indexes. The patients were divided into three groups according to the change in LVEF. The first group was categorized as having a > 10% increase in LVEF, the second group as < 10% improvement in LVEF, and the last group as the same or reduced LVEF. All echocardiographic evaluations were made by an experienced cardiologist blinded to the study protocol.

Statistical analysis

SPSS software version 21.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Whether the values were distributed normally was determined by visual and analytical methods. The study groups were compared using the independent sample t-test/one-way ANOVA for continuous variables with normal distribution, and the Mann Whitney U/Kruskal-Wallis H test for continuous variables without normal distribution. Categorical data were compared with the chi-square test. Logistic regression analysis was performed to determine the independent predictors of LVEF recovery. In order to investigate the group effect for significant numerical values of GDF-15, baseline LVEF, and symptom-to-balloon time, cut-off values were determined and high/low classification was made. Since different methods and kits have been used for the measurement of GDF-15 in previous studies, the cut-off value has not clearly been stated in the literature. Therefore, the grouping for GDF-15 level was made according to receiver operating characteristic (ROC) curve analysis for the ability of GDF-15 to predict LVEF improvement (Figure 1). Youden's index was used to derive the best cut-off value for GDF-15 level. The patients were divided into two groups as high and low GDF-15 on the basis of this value (1.14 ng/ml). The same cut-off value determination was performed for baseline LVEF and symptom-to-balloon time, and the group effect in terms of the predictive value of LV recovery was investigated with values obtained from ROC curve analysis, including 42% for LVEF and 270 minutes for the symptom-to-balloon time. A p-value < 0.05 was considered to be statistically significant.

RESULTS

All of the included patients were evaluated with control echocardiographic examinations after 12-18 weeks. The patients were divided into three groups according

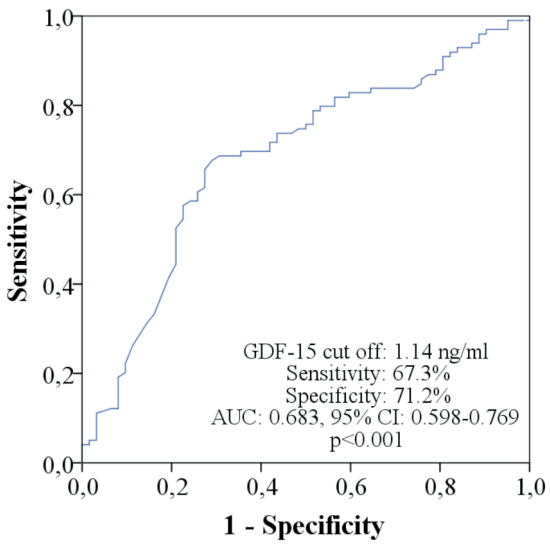

Figure 1. *Receiver operating characteristics curve showing the distinguishing ability of growth differentiation factor 15 level for left ventricular recovery. AUC, area under the ROC curve; CI, confidence interval; GDF-15, growth differentiation factor 15.*

to the change in LVEF: 62 patients (38.5%) had LVEF improvement ≥ 10%, 47 patients had LVEF improvement 1-9% (29.2%), and 52 patients (32.3%) had the same or reduced LVEF. Table 1 shows the baseline clinical characteristics of the three groups. There were no significant differences between the groups in any of the parameters apart from GDF-15 level. Moreover, the difference in ST segment resolution did not reach significance among the groups. However, the higher the resolution, the better LVEF was found in the baseline echocardiography (43.7 ± 4.2 vs. 41.9 ± 7.3 vs. 38.9 ± 6.9, p = 0.004).

Angiographic features of the patients and the parameters obtained by echocardiography performed within 72 hours after the percutaneous coronary procedure were evaluated according to the groups (Table 2). A mean 19.8% increase in LVEF was achieved in patients with LV recovery. This rate was 6.8 ± 2.1% in patients with mild improvement, and -7.0 ± 4.7% in the group with reduced LVEF. There was a significant difference in baseline LVEF

Table 1. Baseline clinical characteristics according to improvement in left ventricular ejection fraction

	Change in LVEF over 12-18 weeks			p value
	≥ 10% (N = 62)	1% to 9% (N = 47)	≤ 0% (N = 52)	
Age, years	58 (52, 65)	60.0 (53.0, 65.0)	63 (53, 71)	0.231
BMI, kg/m^2	27.4 (24.4, 30.8)	26.0 (24.6, 30.4)	27.1 (24.8, 30.3)	0.706
Female, n (%)	11 (17.7)	7 (14.9)	14 (26.9)	0.282
Hypertension, n (%)	22 (35.5)	17 (36.2)	26 (50.0)	0.227
DM, n (%)	13 (21.0)	10 (21.3)	19 (36.5)	0.113
Smoking, n (%)	43 (69.4)	32 (68.1)	30 (57.7)	0.380
Prior CABG, n (%)	1 (1.6)	3 (6.4)	3 (5.8)	0.399
Prior PCI, n (%)	6 (9.7)	4 (8.5)	7 (13.5)	0.696
GFR, ml/dk/1.73 m^2	82.5 (55.7, 110.2)	91 (74, 107)	75.5 (46, 103)	0.133
Previous angina, n (%)	33 (53.2)	18 (38.3)	17 (32.7)	0.070
SBP, mm/Hg	120 (110, 140)	130 (120, 150)	130 (112, 150)	0.334
DBP, mm/Hg	70 (67, 80)	75 (70, 80)	80 (61, 89)	0.688
Heart rate, bpm	81 (67, 88)	79 (66, 90)	80.5 (70, 91.5)	0.576
ECG resolution, n (%)				0.209
Complete resolution	27 (43.5)	17 (36.2)	15 (28.8)	
Partial resolution	29 (46.8)	20 (42.6)	24 (46.2)	
No resolution	6 (9.7)	10 (21.3)	13 (25.0)	
CK-MB, ng/ml	113.4 (45.5, 192.5)	86.7 (47.8, 222.2)	107.9 (46.1, 107.9)	0.878
Troponin, ng/ml	3.66 (2.34, 7.43)	2.97 (1.26, 7.13)	3.20 (0.97, 8.57)	0.610
CRP, mg/dl	10.6 (5.6, 41.5)	12.7 (5.2, 22.9)	15.3 (5.9, 30.7)	0.582
GDF-15, ng/ml	1.00 (0.83, 1.17)	1.07 (0.81, 1.26)	1.24 (1.22, 1.27)	< 0.001

BMI, body mass index; bpm, beat per minute; CABG, coronary artery bypass graft; CK-MB, creatinin kinaz-MB; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiography; GDF-15, growtth differentiation factor-15; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

Table 2. Angiographic and echocardiographic characteristics according to improvement in LVEF

	Change in LVEF over 12-18 weeks			p value
	≥ 10% (N = 62)	1% to 9% (N = 47)	≤ 0% (N = 52)	
Change in LVEF, %	17 (13, 23)	7 (5, 8)	-6 (-4, -9)	< 0.001
Baseline LVEF, %	42 (37, 46)	44 (38, 48)	45 (40, 49)	0.016
LVEF group, n (%)				0.813
41-50%	35 (56.5)	29 (61.7)	35 (67.3)	
31-40%	21 (33.9)	14 (29.7)	14 (26.9)	
≤ 30%	6 (9.7)	4 (8.5)	3 (5.7)	
Baseline LVEDVI, ml/m^2	41.6 (34.8, 50.9)	41.2 (35.1, 52.8)	39.1 (35.4, 49.7)	0.380
Baseline LVEDD, mm	50.0 (46.0, 52.2)	49 (47, 52)	47 (45, 50)	0.085
Baseline LVESVI, ml/m^2	23.4 (18.0, 31.3)	22.3 (19.4, 29.3)	21.2 (17.3, 26.9)	0.166
Baseline LVESD, mm	35.5 (30.7, 39.2)	34.0 (31.5, 38.2)	33.0 (28.3, 37.4)	0.101
PWT, mm	11 (10, 12)	11 (11, 12)	12 (11, 12)	0.060
Baseline WMSI	1.56 (1.43, 1.76)	1.43 (1.25, 1.68)	1.31 (1.18, 1.62)	0.003
Predilatation, n (%)	49 (79.0)	36 (76.6)	42 (80.8)	0.878
Postdilatation, n (%)	28 (45.2)	16 (34.0)	16 (30.8)	0.246
Killip Class > 1, n (%)	16 (25.8)	9 (19.1)	14 (26.9)	0.622
Culprit artery, n (%)				0.406
LAD	31 (50.0)	19 (40.4)	22 (42.3)	
CX	11 (17.7)	6 (12.8)	9 (17.3)	
RCA	20 (32.3)	19 (40.4)	20 (38.5)	
Saphenous vein graft	0 (0)	3 (6.4)	1 (1.9)	
Stent length, mm	18 (15, 26)	18 (15, 25)	20 (15, 28)	0.185
Stent diameter, mm	3.0 (2.75, 3.5)	3 (2.75, 3)	3 (2.75, 3.5)	0.955
Pre-TIMI flow, n (%)				0.015
0/1	39 (62.9)	33 (70.3)	44 (84.6)	
2	15 (24.2)	4 (8.5)	3 (5.8)	
3	8 (12.9)	10 (21.3)	5 (9.6)	
Drug eluting stent, n (%)	43 (69.4)	31 (66.0)	38 (73.1)	0.743
Symptom-to-baloon time (min)	260 (208, 337)	298 (265, 423)	322 (253, 555)	0.011
Final TIMI flow, n(%)				0.008
2	5 (8.1)	6 (12.8)	15 (28.8)	
3	57 (91.9)	41 (87.2)	37 (71.2)	

CX, circumflex artery; LAD, left anterior descendin artery; LVEDD, left ventricular end diastolic diameter; LVEDVI, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESVI, left ventricular end systolic volume index; PWT, posterior wall thickness; RCA, right coronary artery; WMSI, wall motion score index.

between the groups, and baseline LVEF was lower in the patients who had LV recovery [42% (37-46%) vs. 45% (39-48%), p = 0.005]. Moreover, the WMSI score increased as the LV improvement rate increased (≥ 10% vs. ≤ 0%, p = 0.006, 1-9% vs. ≤ 0%, p = 0.050). Pre-PCI TIMI flow 0-1 reduced the rate of LV improvement, while post-PCI TIMI flow 3 increased the LV improvement rate. Statistical differences for both were detected among the groups (p = 0.017, p = 0.004, respectively). In addition, as the symptom-to-balloon time increased, LV improvement decreased (LVEF ≥ 10% group median 268 minutes vs. LVEF ≤ 0% group median 322 minutes, p = 0.018).

Table 3 shows the medical treatment of the patients before the event and after discharge. There were no significant differences between the LV improvement groups in terms of medical treatments. Medical treatment rates after discharge were as follows: acetylsalicylic acid 95.7%; clopidogrel, 11.8%, ticagrelor 88.2%; beta-blockers, 80.1%; RAS inhibitors 68.3%; statins, 93.7%.

High GDF-15 and low GDF-15 groups were generated according to the cut-off value, and follow-up and baseline echocardiographic values were compared be-

Table 3. Prehospitalization and discharge medications according to improvement in left ventricular ejection fraction

	Change in LVEF over 12-18 weeks			p value
	≥ 10% (N = 62)	1% to 9% (N = 47)	≤ 0% (N = 52)	
Medical use pre-PCI, n (%)				
Aspirin	9 (14.5)	6 (12.8)	13 (25.0)	0.207
Clopidogrel	2 (3.2)	4 (8.5)	3 (5.8)	0.492
Ticagrelor	1 (1.6)	0 (0)	0 (0)	0.448
Beta blocker	7 (11.3)	4 (8.5)	11 (21.2)	0.148
ACE inhibitors/ARB	13 (21.0)	13 (27.7)	20 (38.5)	0.118
Calcium antagonists	10 (16.1)	3 (6.4)	7 (13.5)	0.300
Nitrat	1 (1.6)	1 (2.1)	2 (3.8)	0.735
Statin	9 (30.6)	10 (21.3)	17 (32.7)	0.409
Aldosterone antagonisits	1 (1.6)	2 (4.3)	1 (1.9)	0.647
SGLT-2 inhibitors	3 (4.8)	2 (4.3)	2 (3.8)	0.966
Medical use post-PCI, n (%)				
Aspirin	59 (95.2)	45 (95.7)	50 (96.2)	0.966
Clopidogrel	6 (9.7)	4 (8.6)	9 (17.4)	0.268
Ticagrelor	56 (90.3)	43 (91.4)	43 (82.6)	0.396
Beta blocker	48 (77.4)	29 (83.0)	42 (80.8)	0.764
ACE inhibitors/ARB	38 (61.3)	36 (76.6)	36 (69.2)	0.232
Calcium antagonists	3 (4.8)	5 (10.6)	8 (15.4)	0.169
Nitrat	3 (4.8)	2 (4.3)	6 (11.5)	0.261
Statin	60 (96.8)	43 (91.5)	48 (92.3)	0.456
Aldosterone antagonisits	9 (14.5)	6 (12.8)	4 (7.7)	0.516
SGLT-2 inhibitors	5 (8.1)	4 (8.5)	6 (11.5)	0.797

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SGLT-2, sodium-glucose co-transporter-2.

tween the two groups. The ratio of follow-up/baseline LVEDVI was 0.96 in the low GDF-15 group and 1.04 in the high GDF-15 group (p < 0.001). The same statistical difference was also detected for LVESVI (low GDF-15 = 0.96, high GDF-15 = 1.10, p < 0.001). The follow-up/baseline LVEF ratio was higher in the low GDF-15 group (1.13 vs. 1.03, p < 0.001). In parallel, the WMSI ratio was also lower in the low GDF-15 group (0.89 vs. 0.96, p < 0.001) (Figure 2). When the GDF-15 groups were compared according to ST-segment resolution ratios, there was no difference between the groups (high GDF-15 group; complete resolution 33.0%, partial resolution, 47.3%, no resolution, 19.8% / low GDF-15 group; complete resolution 41.4%, partial resolution, 42.9%, no resolution, 15.7%, p = 0.521).

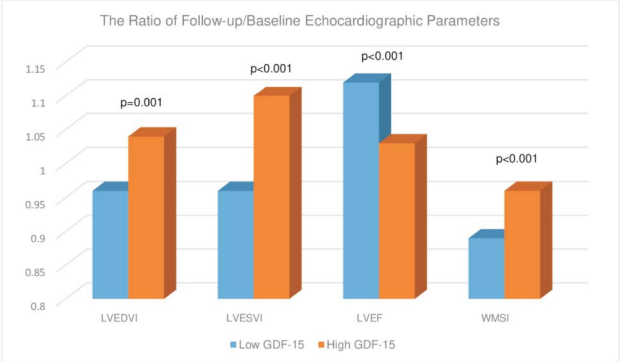

Figure 2. *Bar graph showing the change in left ventricular function and volume after percutaneous coronary intervention. The ratio of follow-up/baseline echocardiographic parameters detected. LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; WMSI, wall motion score index.*

Logistic regression analysis was performed to examine the independent predictors of LV recovery. Low baseline LVEF [odds ratio (OR): 0.85, 95% confidence interval (CI) 0.82-0.94, p = 0.001], low GDF-15 (OR: 0.79, 95% CI 0.68-0.93, p = 0.004), presence of previous angina (OR: 2.34, 95% CI 1.10-4.96, p = 0.027), pre PCI TIMI flow 0-1 (OR: 0.31, 95% CI 0.13-0.70, p = 0.009) and long symptom-to-balloon time (OR: 0.97, 95% CI 0.95-1.00, p = 0.043) were determined to be independent predictors

of LV recovery (Table 4).

Cut-off values were determined for baseline LVEF, GDF-15 and symptom-to-balloon time as independent predictors (Figure 1). According to the ROC curve analysis, the cut-off value for LVEF was 42% [area under the curve (AUC) 0.643, 95% CI 0.545-0.716, p = 0.005], the cut-off value for symptom-to-balloon time was 270 minutes (AUC 0.651, 95% CI 0.550-0.731, p = 0.002), and the cut-off value for GDF-15 was 1.14 ng/ml (AUC 0.683, 95% CI 0.598-0.769, p < 0.001). Consequently, low baseline LVEF (OR: 2.24, 95% CI 1.08-4.66, p = 0.021), low symptom-to-balloon time (OR: 2.59, 95% CI 1.27-5.30, p = 0.006) and low GDF-15 level (OR: 2.93, 95% CI 1.43-6.02, p = 0.001) were associated with LV recovery (Table 4).

Table 4. Independent predictors of left ventricular improvement

Variables	Odds ratio	95% CI	p value
First model*			
Baseline LVEF (per 1%)	0.85	[0.82, 0.94]	0.001
TIMI 0-1 flow pre-PCI	0.32	[0.13, 0.70]	0.009
GDF-15 (per 1 ng/ml)	0.79	[0.68, 0.93]	0.004
Previous angina	2.34	[1.10, 4.96]	0.027
Symptom-to-baloon time (min)	0.97	[0.95, 1.00]	0.043
Second model#			
Low LVEF	2.24	[1.08, 4.66]	0.021
Long symptom-to-baloon time	2.59	[1.27, 5.30]	0.006
Low GDF-15	2.93	[1.43, 6.02]	0.001

CI, confidence interval; GDF-15, growth differentiation factor-15; LVEF, left ventricular ejection fraction; min, minutes; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

* In the first model, LVEF, GDF and symptom-to-balloon time were numerically placed in regression analysis. # In the second model, LVEF, GDF-15 and symptom-to baloon time were categorized and placed in regression analysis. Classification as high/low was made using the cut off values obtained from the ROC analysis, 42% for LVEF, 270 min for symptom to baloon time, and 1.14 ng/ml for GDF-15.

DISCUSSION

The important findings of our study are as follows: (a) 38.5% of STEMI patients who underwent successful PCI had ≥ 10% improvement in LVEF, 29.2% of the patients had LVEF improvement between 1-9%, and LVEF remained the same or reduced in 32.3% of the patients; (b) a symptom-to-balloon time < 270 min was associated with a 2.5-fold higher rate of LVEF recovery, baseline LVEF ≤ 42% was associated with a 2.2-fold higher rate of LVEF recovery, pre-PCI TIMI flow = 2/3 was associated with a 3.1-fold higher rate of LVEF recovery, and the presence of previous angina was associated with a 2.3-fold higher rate of LVEF recovery; (c) being in the low GDF-15 group was associated with LV recovery (OR: 2.93, 95% CI 1.43-6.02, p = 0.001); (d) lower LVEDVI, LVESVI and WMSI ratios were obtained in the follow-up/baseline echocardiographic comparisons in the low GDF group.

Despite receiving successful revascularization and guideline-recommended standard treatment, a significant portion of patients do not have the expected improvement in LV function.[16] Large cohort studies have reported that 21-42% of patients did not have LV improvement,[17] which is consistent with our findings (LV function remained the same or reduced in 32.3% of the patients).

Increased cardiac mortality has been observed in long-term follow-up in patients without improvement in LVEF after MI.[16,18] Although the relationship between prognosis and baseline LVEF and long-term LV remodeling is known, studies showing the effect of short-term LVEF change on clinical outcomes are limited. LVEF non-recovery has been associated with a 6-fold increase in sudden cardiac death and 4-fold increase in all-cause mortality.[17] Moreover, another study reported that mortality was 3 times higher in patients without LV improvement.[19] Parodi et al. reported that a ≥ 10% increase in LVEF at 3-6 months follow-up was considered as a net improvement, and the survival rates of the group with net improvement were more than 2 times higher than those without improvement in LVEF (8% vs. 18%, p = 0.002).[20] We determined the cut-off value for LV recovery as 10% in our study, considering that LVEF < 10% change would not be considered as LVEF recovery due to variations in the measurement.

GDF-15, a member of the TGF-beta family, is a molecule that is found in a small amount in the blood and is released from many different tissues in stress situations.[21] It has been demonstrated that stress factors such as cardiac instability, inflammation, ischemia and volume overload trigger GDF-15 synthesis.[22] Evidence at the molecular and cellular level indicates that GDF-15 significantly contributes to cardioprotection through multiple signal

pathways in these stressful situations.[23] Some studies have shown that elevated plasma GDF-15 concentrations protect endothelial cells from cellular damage via the PI3K/AKT/eNOS pathway and by inhibiting ROS-induced activation of NF-jB/JNK cascade.[24] In addition, GDF-15 has been reported to provide antihypertrophic and anti-apoptotic effects by activating ALK type 1 receptors and by inhibiting epidermal growth factor receptor (EGFR) transactivation.[23]

Many studies have investigated the prognostic value of high GDF-15 levels in acute coronary syndrome patients, and it has been determined that GDF-15 can predict adverse events in STEMI patients.[12] In the Merlin TIMI study, GDF-15 was an independent predictor of cardiovascular (CV) death and heart failure in non-STEMI patients, and the addition of GDF-15 to the TIMI score provided additional independent information about the prognosis.[25] In the Framingham study, patients with GDF-15 were followed for 11.4 years. The high GDF-15 group had a 3-fold increased rate of death, 6-fold increased rate of heart failure and 2-fold increased rate of CV events, indicating that GDF-15 can provide valuable prognostic information over the long term.[26] It has also been shown that GDF-15 can predict CV diseases in healthy women independently of C-reactive protein (CRP) and other CV risk factors, so it is thought that GDF-15 uses different pathways.[27] Thus, the elevation of GDF-15 even in a subclinical state suggests that it could be used for prognosis even before the disease is fully settled. Our study was not a long-term prognosis study, however we determined the relationship between alterations in cardiac function during 12-18 weeks and GDF-15, highlighting the importance of the molecule.

Change in LVEDVI is an important determinant of CV mortality in HF patients.[28] A few studies have examined LV remodeling and GDF-15 in STEMI patients. In these studies, LVEDVI ratios were compared according to GDF-15 levels. There were no differences in volume indexes compared to GDF-15 levels, but higher HF and mortality were found in patients with high GDF-15, and thus there was a contrast between clinical outcomes and echocardiographic values.[29] While more heart failure was observed, the lack of statistically significant change in diastolic volumes suggests that the results should be evaluated carefully. The authors of the study emphasized in the limitations that the study was neither designed nor powered for the effects of GDF-15 on LV remodeling. Therefore, it should remain at the hypothesis stage. In another study, the relationship between GDF-15 and reverse modeling after MI was investigated. A 20% increase in LVEDV was accepted as LV adverse remodeling, and they found a relationship between the presence of LV adverse remodeling and high GDF-15 values (OR 10.1, 95% CI 2.5-40.1, $p < 0.001$).[30] This is consistent with our results of a 10% increase in LVESVI and 4% increase in LVEDVI in the high GDF-15 group. Besides, there was no significant improvement in LVEF in the high GDF-15 group (3%), while there was a 13% increase in LVEF in the low GDF-15 group in our study. This suggests that the patients with a high level of GDF-15 were at a higher risk for post-MI HF.

Baseline low LVEF was found to be an important predictor of LV recovery in our study (OR: 0.85 95% CI 0.82-0.94, $p = 0.001$). Moreover, baseline LVEF $\leq$ 42% was associated with a 2.5-fold higher rate of LVEF recovery. Consistent with our findings, Serrao et al. found that 42% of their patients had adverse remodeling at 13 months of follow-up, and that patients with reverse modeling had a lower baseline LVEF.[8] There could be several possible reasons for these findings. Better LV improvement in patients with low baseline LVEF may be related to having more stunned myocardium, which could potentially improve. Some patients had a higher baseline LVEF reduction and LV systolic dysfunction than expected according to MI region and achieved normal flow with successful reperfusion, suggesting that dysfunctional myocardium became viable over time, and that the stunned myocardium area was larger. Another possibility is that hyperkinesia in areas without damage in the early post-MI period can lead to a higher than normal LVEF measurement, which may affect subsequent echo evaluations.

The presence of previous angina was found to be an independent predictor of LV recovery in our study (OR: 2.34, 95% CI 1.10-4.96, $p = 0.027$). Patients with previous angina have been shown to have less LV adverse remodeling and smaller infarct size.[31] Many mechanisms may be the cause of this situation, which is also known as ischemic preconditioning. Studies related to ischemic preconditioning have reported that it is predictive of cardiac recovery generally, although there are partially conflicting results.[32]

The infarct area can be reduced and better LV improvement can be achieved by saving more myocardium in patients who undergo percutaneous coronary procedures in the early period.[33] According to their study, 1-year mortality was higher in patients with a > 4 hour symptom-to-balloon time (OR: 1.55, 95% CI 1.01-2.4, p < 0.001). A symptom-to-balloon time < 270 min was determined as the cut-off value for LV recovery in our study, and below this cut-off value, a 2.5-fold higher rate of LV recovery was detected. A short symptom-to-balloon time contributed to post PCI TIMI flow 3 (p = 0.012).[33] Although there was no statistical relationship between the symptom-to-balloon time and the presence of post-TIMI flow 3 in our study, the presence of post-TIMI flow 3 in univariate analysis predicted LV recovery (OR: 0.190, 95% CI 0.062-0.581, p = 0.004), however it did not reach statistical significance in multivariate analysis (OR: 0.450, 95% CI 0.144-1.403, p = 0.109). The exclusion of patients with post-PCI TIMI flow 0-1 from the study may have led to different results. In addition, the presence of coronary microcirculation is an important predictor of LV systolic function. For this reason, even if TIMI flow 3 is supplied, if the microcirculation cannot be achieved, there may be wall motion defects and consequently loss of LV function.

In our study, approximately 70% of the patients were given angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), and approximately 80% of the patients received beta-blocker treatment after the procedure. However, no relationship was established between LV recovery and medical treatment. There could be several possible reasons for this. First, the number of patients was small and the follow-up period was limited to see the effect of these drugs on remodeling. Moreover, while it is necessary to reach the maximum dose to affect remodeling, the patients were discharged with doses at the level of 40% of the maximum dose for ACE inhibitors/ARBs and 55% of the maximum dose for beta-blockers. As a result, the low number of patients, the short follow-up period and the inability to reach the maximum dose may have prevented the positive effects of these treatments on cardiac dimensions and function.

There are several limitations to this study. First, keeping the GDF-15 samples at -80 °C for a long time may have ruined stability. Second, while there are many methods to measure cardiac function, we used echocardiography. Neither cardiac magnetic resonance imaging nor echocardiographic strain which detect myocardial fibrosis better, was performed to identify cardiac regions with potentially different fibrosis patterns. In some patients, failure to see the endocardium accurately may raise suspicion about the accuracy of the data. In addition, since the improvement in LVEF was evaluated categorically rather than numerically, this may also by a limitation. However, it is clear that this method of administration is simpler and more useful. Third, the use of sodium-glucose co-transporter-2 inhibitors in a limited number of patients and the absence of the use of angiotensin receptor-neprilysin inhibitors prevented us from seeing whether these medications have an effect on LV recovery. Fourth, patients who did not come for control examinations were excluded from the study. In these patients, the reason for missing the control examination could be a non-stable clinical condition due to decreased LVEF. For this reason, the exclusion of these patients may have created selection bias. Moreover, patients with cardiac mortality were excluded from the study, which may have affected our results. Fifth, there is no clear cut-off value determined for GDF-15 in the literature, so we made a classification according to our study population. In addition, the GDF-15 values of the patients in our study were slightly lower than in the literature, probably due to the different baseline characteristics and the inclusion criteria. Finally, repeating GDF-15 measurements would have given us an idea of the dynamic changes in the infarct myocardium, however we did not perform repeat measurements in this study.

CONCLUSIONS

In this study, we showed that baseline LVEF, presence of previous angina, pre-PCI TIMI flow, symptom-to-balloon time and GDF-15 were independent predictors of LV recovery in STEMI patients who underwent successful PCI. Moreover, more adverse remodeling was detected in patients with high GDF-15 levels. Nevertheless, prospective controlled trials are needed for GDF-15 to guide patient management and treatment selection, in addition to other biomarkers and clinical predictors. Patients with increased GDF-15 concentrations could po-

tentially benefit from anti-inflammatory, antioxidant or antiaging therapies, considering the functioning mechanism of GDF-15. New treatment goals may emerge with a better understanding of the pathways where GDF-15 is located.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

No funding was received for this research.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Executive summary: heart disease and stroke statistics—2016 update. *Circulation* 2016;133:447-54.
2. Puymirat E, Simon T, Steg PG, et al. Association of changes in clinical characteristics and management with improvement in survival among patients with ST elevation myocardial infarction. *JAMA* 2012;308:998-1006.
3. Zandecki L, Janion M, Sadowski M et al. Associations of changes in patient characteristics and management with decrease in mortality rates of men and women with ST-elevation myocardial infarction - a propensity score-matched analysis. *Arch Med Sci* 2020;16:772-80.
4. Bolognese L, Neskovic AN, Parodi G, et al. Left ventricular remodeling after primary coronary angioplasty: patterns of left ventricular dilation and long-term prognostic implications. *Circulation* 2002;106:2351-7.
5. Ola RK, Meena CB, Ramakrishnan S, et al. Detection of left ventricular remodeling in acute ST elevation myocardial infarction after primary percutaneous coronary intervention by two dimensional and three dimensional echocardiography. *J Cardiovasc Echogr* 2018;28:39-44.
6. Camici PG, Prasad SK, Rimoldi OE. Stunning, hibernation, and assessment of myocardial viability. *Circulation* 2008;117:103-14.
7. Benz DC, von Dahlen AP, Huang W, et al. No differences in rest myocardial blood flow in stunned and hibernating myocardium: insights into the pathophysiology of ischemic cardiomyopathy. *Eur J Nucl Med Mol Imaging* 2019;46:2322-8.
8. Serrao GW, Lansky AJ, Mehran R, Stone G. Predictors of left ventricular ejection fraction improvement after primary stenting in ST-segment elevation myocardial infarction (from the harmonizing outcomes with revascularization and stents in acute myocardial infarction trial). *Am J Cardiol* 2018;121:678-83.
9. Shin MY, Kim JM, Kang YE, et al. Association between growth differentiation factor 15 (GDF15) and cardiovascular risk in patients with newly diagnosed type 2 diabetes mellitus. *J Korean Med Sci* 2016;31:1413-8.
10. Chan MM, Santhanakrishnan R, Chong JP, et al. Growth differentiation factor 15 in heart failure with preserved vs. reduced ejection fraction. *Eur J Heart Fail* 2016;18:81-8.
11. Khan SQ, Ng K, Dhillon O, et al. Growth differentiation factor-15 as a prognostic marker in patients with acute myocardial infarction. *Eur Heart J* 2009;30:1057-65.
12. Eitel I, Blase P, Adams V, et al. Growth-differentiation factor 15 as predictor of mortality in acute reperfused ST-elevation myocardial infarction: insights from cardiovascular magnetic resonance. *Heart* 2011;97:632-40.
13. Bodde MC, Hermans M, Laarse A, et al. Growth differentiation factor-15 levels at admission provide incremental prognostic information on all-cause long-term mortality in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. *Cardiol Ther* 2019;8:29-41.
14. Rueda F, Lupon J, Garcıa-Garcıa C, et al. Acute-phase dynamics and prognostic value of growth differentiation factor-15 in ST-elevation myocardial infarction. *Clin Chem Lab Med* 2019;57:1093-101.
15. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1.e14-39.e14.
16. Ottervanger JP, van't Hof AW, Reiffers S, et al. Long-term recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *Eur Heart J* 2001;22:785-90.
17. Chew DS, Heikki H, Schmidt G, et al. Change in left ventricular ejection fraction following first myocardial infarction and outcome. *JACC Clin Electrophysiol* 2018;4:672-82.
18. Ndrepepa G, Mehilli J, Martinoff S, et al. Evolution of left ventricular ejection fraction and its relationship to infarct size after acute myocardial infarction. *J Am Coll Cardiol* 2007;50:149-56.
19. Chew DS, Wilton SB, Kavanagh K, et al. Left ventricular ejection fraction reassessment post-myocardial infarction: current clinical practice and determinants of adverse remodeling. *Am Heart J* 2018;198:91-6.
20. Parodi G, Memisha G, Carrabba N, et al. Prevalence, predictors, time course, and long-term clinical implications of left ventricular functional recovery after mechanical reperfusion for acute myocardial infarction. *Am J Cardiol* 2007;100:1718-22.
21. Zimmers TA, Jin X, Hsiao EC, et al. Growth differentiation factor-15/macrophage inhibitory cytokine-1 induction after kidney and lung injury. *Shock* 2005;23:543-8.
22. Taddei S, Virdis A. Growth differentiation factor-15 and cardiovascular dysfunction and disease: malefactor or innocent bystander? *Eur Heart J* 2010;31:1168-71.
23. Arkoumani M, Papadopoulou-Marketou N, Nicolaides NC, et al.

The clinical impact of growth differentiation factor-15 in heart disease: a 2019 update. *Crit Rev Clin Lab Sci* 2020;57:114-25.
24. Li J, Yang L, Qin W, et al. Adaptive induction of growth differentiation factor 15 attenuates endothelial cell apoptosis in response to high glucose stimulus. *PLoS One*. 2013;8:e65549.
25. Antman EM, Cohen M, Bernink P, et al. The TIMI risk score for unstable angina/non-ST elevation MI. *JAMA* 2000;284:835-42.
26. Wang TJ, Wollert KC, Larson MG, et al. Prognostic utility of novel biomarkers of cardiovascular stress the Framingham Heart Study. *Circulation* 2012;126:1596-604.
27. Brown DA, Breit SN, Buring J, et al. Concentration in plasma of macrophage inhibitory cytokine-1 and risk of cardiovascular events in women: a nested case-control study. *Lancet* 2002;359:2159-63.
28. Wong M, Staszewsky L, Latini R, et al. Severity of left ventricular remodeling defines outcomes and response to therapy in heart failure: valsartan heart failure trial (Val-HeFT) echocardiographic data. *J Am Coll Cardiol* 2004;43:2022-7.
29. Lin JF, Wu S, Hsu SY, et al. Growth-differentiation factor-15 and major cardiac events. *Am J Med Sci* 2014;347:305-11.
30. Dominguez-Rodriguez A, Abreu-Gonzalez P, Avanzas P. Relation of growth-differentiation factor 15 to left ventricular remodeling in ST-segment elevation myocardial infarction. *Am J Cardiol* 2011;108:955-8.
31. Solomon SD, Anavekar NS, Greaves S, et al. Angina pectoris prior to myocardial infarction protects against subsequent left ventricular remodeling. *J Am Coll Cardiol* 2004;43:1511-4.
32. Zahn R, Schiele R, Schneider S, et al. Effect of preinfarction angina pectoris on outcome in patients with acute myocardial infarction treated with primary angioplasty. *Am J Cardiol* 2001;87:1-6.
33. De Luca G, Suryapranata H, Zijlstra F, et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol* 2003;42:991-7.