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Features of the Growth factor of differetiation-15 in patients with acute myocardial infarction

Khorolets E.V., Shlyk S.V.

Rostov State Medical University, Rostov-on-Don, Russia

Authors

Ekaterina V. Khorolets*, M.D, PhD, Associate Professor of the Department of Internal Medicine, Rostov State Medical University, Rostov-on-Don, Russia.

Sergey V. Shlyk, M.D, PhD, Professor, Head of the Department of Internal Medicine, Rostov State Medical University Ministry, Rostov-on-Don, Russia.

Abstract

Objective *of the current study was to the clinical and laboratory features and the level of growth differentiation factor 15 (GDF-15) in patients with acute ST-segment elevation myocardial infarction (STEMI) at the inpatient stage of treatment.*

Materials and methods. *Clinical and laboratory characteristics of STEMI patients were assessed during the hospital stay; echocardiography was also performed. The prognosis of in-hospital mortality was calculated using the GRACE scale. Statistical analysis was performed using the statistical software package «Statistica 10.0 for Windows».*

Results. *The GDF-15 level increases on the first day of STEMI and correlates with the risk of in-hospital mortality according to the GRACE scale. STEMI patients with GDF-15 values≥1200 ng/ml doesn't reach the reference values during inpatient treatment. Patients with an unfavorable in-hospital outcome of STEMI were at a high risk of in-hospital mortality according to the GRACE scale with a tendency to GDF-15 concentration rise. Myocardial contractility of the left ventricle was also reduced in these patients.*

Conclusion. *The persistence of high GDF-15 values during the in-patient treatment determines the prognosis of STEMI.*

Key words: *acute myocardial infarction, GDF-15.*

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* Corresponding author. Tel. +79034335477. E-mail: kata_maran@mail.ru

Patients with acute ST-segment elevation myocardial infarction (STEMI) are at high risk of early complications. That leads to higher pre-hospital and in-hospital mortality. Outcomes depend on present risk factors, time when the patient started seeking medical help, access to coronary angiography (CAG), surgical treatment. Currently, STEMI is still investigated in experiments and real clinical settings.

Experiments have shown that STEMI is associated with increased levels of growth differentiation factor 15 (GDF-15) in cardiac myocytes. GDF-15 regulates late activation of macrophages, had anti-inflammatory effects, and reduces macrophage-to-foam-cell transformation. GDF-15 also has some protective effects of myocardium even before the first clinical manifestations of MI, but also increases the risk of cardiovascular disease. It can be also found in atherosclerotic plaques in MI [1].

Mimeault M. et al. (2010) have suggested that GDF-15 has the effects as antiatherogenic cytokine as it inhibits expression and activity of lipoprotein lipase and low-density lipoprotein receptors. However, the data are controversial. Low levels of GDF-15 increase the progression of atherosclerosis, and extremely high levels of GDF-15 are associated with atherosclerotic vessel damage and the development of ischemia [2].

In-hospital treatment of STEMI still needs to be investigated further, as well as risk factors and laboratory and instrumental outcome predictors.

Objective of the current study was to the clinical and laboratory features and the level of GDF-15 in patients with STEMI at the inpatient stage of treatment.

Material and methods

The current study included 150 patients with STEMI. The study was performed in accordance with the Good Clinical Practice standards and the Helsinki declaration principles. According to the 2007 Russian Society of Cardiology guidelines, STEMI diagnosis had to be determined with the clinical, ECG and laboratory markers of myocardial ischemia: troponin I, creatine kinase (CK) and creatine kinase MB (CK-MB). Inclusion criteria were age 45 and older, arterial hypertension (AH), first 24 of the disease. Exclusion criteria: type 1 and 2 diabetes, severe kidney failure, liver failure, fertile women, cancer, systemic inflammatory diseases (SIDs), infectious diseases. Physical examination included systolic and diastolic blood pressure measurements (SBP and DBP), heart rate (HR). Laboratory values included alanine transaminase (ALT), aspartate transaminase (AST), urea, creatinine, myocardial necrosis markers, electrolytes, glomerular filtration rate (GFR). Plasma levels of GDF-15 were assessed using the enzyme immunoassay. We used standard Human GDF-15/MIC-1 ELISA ("BioVendor", Czeck Republic) reactive. We also performed echocardiography to assess left atrial (LA), right atrial (RA), left ventricular (LV) sizes, LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), stroke volume (SV), ejection fraction (EF), left pulmonary artery pressure, the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave).

Patients with STEMI were examined at admission to the cardiology department and at discharge. The prognosis of in-hospital mortality was calculated using the GRACE scale (Global Registry of Acute Coronary Events scale):<126 points — low risk (<2%), 126–154 points — moderate risk (2–5%);>154 points — high risk (>5%). Statistical analysis was performed using the statistical software package "Statistica 10.0 for Windows".

Results

General clinical and laboratory characteristics of patients with STEMI are mean age 61.69±0.96 years, SBP 135.42±2.25 mmHg, DBP 81.86±1.21 mmHG, HR 81.61±1.51 beats/min. Laboratory values: ALT 45.03±2.57 Units/l, AST — 86.26±8.73 Units/l, urea 9.76±1.44 mmol/l, creatinine 84.45±2.68 mmol/l, estimated GFR 81.17±1.98 ml/min/1.73m^2. Markers of myocardial necrosis: troponin I 13.22±1.40 ng/ml, CK 320.23±35.56 U/l, MB-CK 61.63±14.92 U/l.

Echocardiography results in the general group: LA — 41.38±0.34 mm, LV ESS — 40.84±0.30 mm, LVEDS 53.43±0.29 mm, LVESV 140.70±1.81 ml, EF 46.11±0.50%, E — 50.19± 0.99 cm/s, A — 60.40± 1.12 cm/s, E/A — 0.91± 0.03, RA — 32.84± 0.21 mm, RV 29.95±0.19 mm, PA pressure 32.46± 0.59 mm Hg. These values signify reduced myocardial contractility, rise of pressure in the pulmonary artery and tendency towards the A wave rise.

All patients with STEMI that were included into our study received initial therapy including dual antiplatelet therapy, anticoagulants, beta-blockers, ACE inhibitors, statins, nitrates. Reperfusion therapy was performed before the patient was admitted to the hospital — pharmacological thrombolysis, surgical — CAG, pharmacoinvasive approach. Some patients had contraindications to thrombolytic and therapy and

CAG, including refusal to get surgical treatment, and received only initial therapy.

Assessment of laboratory markers plays a major role in determining prognosis in patients with STEMI. Retrospective studies have shown that high levels of GDF-15 are associated with higher risk of mortality and/or STEMI in patients with acute coronary syndrome (ACS). GUSTO-IV, FRISC-2, ASSENT-2, and AMI studies have investigated the role of GDF-15 in ACS patient risk stratification [3, 4] at different points of the disease [5, 6] and the length of follow-up.

In the general group of STEMI patients GDF-15 levels in the first 24 hours were 1174.3±85.2 ng/ml, at discharge — 1017.1±114.3 ng/ml ($p>0.05$). Probably, relatively short period of hospital stay was not sufficient to assess the levels of GDF-15 and further studies are required.

During the first 24 hours of STEMI GDF-15 concentration increased above normal limits. Depending on GDF-15 all the patients were divided into GDF-15<1200 and GDF-15≥1200 ng/ml groups (Figure 1). Independently of GDF-15<1200 or GDF-15≥1200 ng/ml during the first 24-hours GDF-15 levels decreased due to in-hospital treatment and the changes were statistically significant. At the same time, patients with STEMI with GDF-15≥1200 ng/ml, GDF-15 concentration hasn't reached its normal levels during the hospital stay.

In general, patients with STEMI and GDF-15≥1200 ng/ml during the first 24 hours of MI haven't reached reference values during hospital stay and that affects their prognosis.

According to Kempf T. et al. (2006), GDF-15 is protective for cardiac myocytes and the rise of its concentration is associated with the body's high cytoprotective abilities [7].

Currently special scales that assess prognosis of patients with ACS and MI at the hospital and during pre-hospital stage of treatment are available. We used GRACE scale. Depending on the risk of in-hospital mortality (low, moderate, severe) we calculated GDF-15 values at admission and discharge (Figure 2). During the first 24 after admission, in patients with STEMI the mean levels of GDF-15 increased together with the risk according to GRACE scale ($p<0.05$). At discharge GDF-15 levels was higher in patients with high risk according to GRACE than in patients at low risk. There were no statistically significant differences in the reduction of GDF-15 concentration during in-hospital treatment.

As such, patients with STEMI, who are at the high risk of in-hospital mortality according to GRACE, GDF-15 is the highest during the first 24 hours after admission and at discharge. During the hospital stay GDF-15 tended to get lower with the higher values in patients at the high risk according to GRACE.

GDF-15 concentration at admission was positively associated with GDF-15 at discharge ((r=0.42, $p<0.05$). At discharge GDF-15 correlated with RA (r=0.37, $p<0.05$) and RV (r=0.29, $p<0.05$) size, PA pressure (r=0.31, $p<0.05$). Higher levels of GDF-15 at admission (r=–0.21, $p<0.05$) and at discharge (r=-0.37, $p<0.05$) was associated with lower LVEF on echocardiography. Echocardiographic values such as decreased LVEF, dilation of right and left chambers increase the risk of cardiac failure in patients with MI at both the in-hospital and pre-hospital treatment stages.

During in-patient treatment 7 patients died (5.3%). The causes included pulmonary edema in 3 patients and cardiogenic shock in 4 patients. The patients were divided into several groups according to the hospital outcome: death or positive outcome.

In patients with negative and positive outcomes age (65.42±4.33 years), SBP (126.66±12.29 mmHg) and DBP (78.33±7.92 mmHg) were comparable; HR

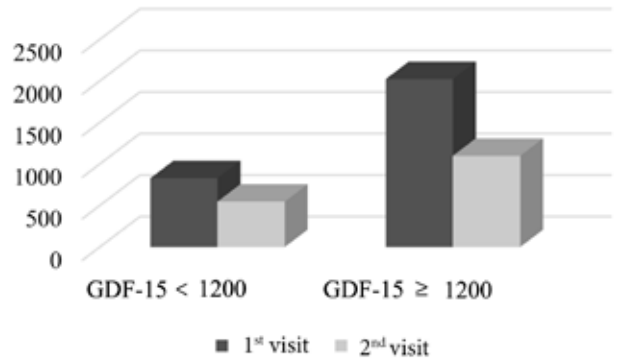

Figure 1. GDF-15 in patients with STEMI from the GDF-15<1200 and GDF-15≥1200 ng/ml groups.
P<0.05 between 1 and 2 visits in GDF-15≥1200 ng/ml group.

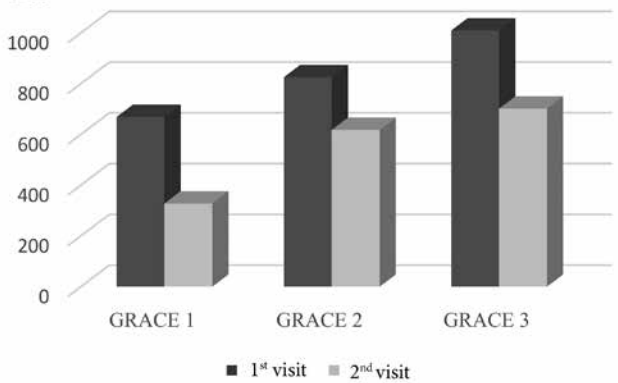

Figure 2. GDF-15 changes during the in-hospital treatment according to GRACE scale (p>0.05).

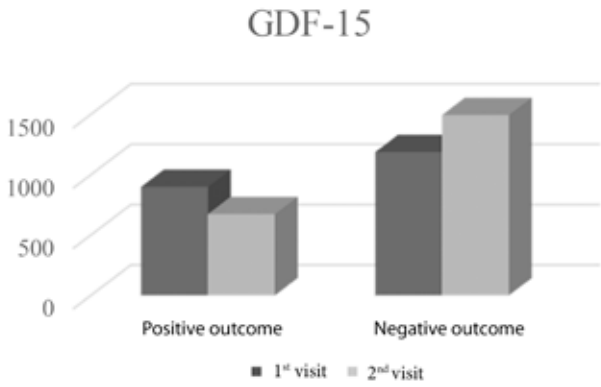

Figure 3. GDF-15 during in-hospital treatment according to outcome.
Note. Positive outcome p=0.09, negative outcome p=0.76.

(98.66±12.80 beats/min) and in-hospital mortality risk according to GRACE scale (204.28±11.48) were higher in the patients with negative outcomes (age 61.51±11.86 years, SBP 135.79±27.56 mmHg, DBP 82.01±14.70 mmHG (p>0.05), HR 80.90±17.63 beats/min, GRACE 163.36±30.63 points (p<0.05)). Patients with negative outcomes also had higher levels of ALT (74.83±21.65 U/l), AST (188.16±85.39 U/l), CK (735.16±323.99 U/l), MB-CK (95.16±41.98 U/l) compared with patients with positive outcomes (AST 98.35±8.29 U/l, ALT 48.70±2.49 U/l, CK — 368.76±33.86 U/l, MB-CK 90.77±15.49 U/l). These data confirms that the larger area of myocardium was affected patients with negative outcomes in the first 24 hours after admission.

Figure 3 shows GDF-15 values in patients with negative and positive outcomes during their hospital stay. Patients with negative outcomes had higher levels of GDF-15 that tended to increase further during in-hospital treatment. GDF-15 in patients with positive STEMI outcomes tended to decrease during in-hospital treatment.

Therefore, patients with negative outcomes have higher levels of GDF-15 that increase further during in-hospital treatment.

We didn't get any statistically significant differences in echocardiographic findings: LA 42.04±0.36 and 42.28±1.13mm, LVESS 41.42±0.31 and 41.71±1.35mm, LVEDS 54.01±0.30 and 53.85±1.37 mm, LVESV 77.79±1.47 and 78.00±6.60 ml, LVEDV 144.31±1.87 and 142.57±8.28 ml, EF 47.25±0.52 and 44.14±1.65%) in patients with STEMI with positive and negative outcomes (p>0.05). Patients with negative outcomes had larger RA — 33.14±0.91mm, RV 29.85±0.51 mm and pressure in PA — 39.28±3.88 mm compared with patients with positive outcomes — RA 33.26±0.22 mm, RV 30.35±0.19 mm, PA pressure — 33.25±0.58 mmHg (p<0.05).

As such, patients with STEMI and negative outcomes had right chambers overload, signs of pulmonary hypertension and decreased myocardial contractility.

Discussion

Assessment of changes in physical examination, laboratory and instrumental findings are crucial for determining the prognosis in STEMI. Khavinson et al (2015) state that increased levels of GDF-15 correlated with the level of LV diastolic dysfunction [9], especially in obese patients [10]. According to our results, GDF-15 increased in patients with STEMI and that was associated with reduction of LV myocardial contractility and RA and RV overload.

Conclusion

Complex assessment of GDF-15 and GRACE scale can be used to predict outcome in hospitalized patients with STEMI. Patients with the higher levels of GDF-15 during the first 24 hours after admission have larger area of myocardial damage, right chambers overload and negative prognosis of in-patient treatment.

Conflict of interest: none declared.

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