

The role of insulin-like growth factor-1 in development of coronary no-reflow and severity of coronary artery disease in patients with acute myocardial infarction

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Abstract

Introduction: Insulin-like growth factor-1 (IGF-1) has atheroprotective effects via reduction in oxidative stress, cellular apoptosis, pro-inflammatory signaling, and endothelial dysfunction.

Aim: We hypothesized that low levels of IGF-1 may be associated with the severity and extent of coronary artery disease and development of the coronary no-reflow phenomenon in patients with acute ST-elevation myocardial infarction (STEMI) and investigated the role of the IGF-1 molecule in the coronary no-reflow phenomenon and severity of coronary artery disease (CAD) in patients with acute STEMI in a tertiary hospital.

Material and methods: The study was conducted among 113 patients undergoing primary percutaneous coronary intervention (PPCI) for STEMI, of whom 49 patients developed the no-reflow phenomenon. Coronary no-reflow was defined as Thrombolysis In Myocardial Infarction (TIMI) flow grade 2 or less after intervention. Insulin-like growth factor-1 levels were measured in both groups. The severity and extent of CAD were evaluated according to the Gensini and Syntax scores.

Results: Although IGF-1 levels were lower in the no-reflow group, there was not a statistically significant difference between the no-reflow group and the control group (116.65 ±51.72 vs. 130.82 ±48.76, $p = 0.130$). Gensini and Syntax scores were higher in the no-reflow group. There was no association between Gensini and Syntax scores and IGF-1 levels ($r = -0.071$, $r = 0.479$, $r = -0.158$, $p = 0.113$).

Conclusions: In this study, IGF-1 levels were not statistically different between patients developing the no-reflow phenomenon and controls. There was no association between development of the no-reflow phenomenon and severity of CAD or IGF-1 levels. Nevertheless, large scale studies are needed to verify these results.

Key words: insulin-like growth factor-1, no-reflow, coronary artery disease, ST-elevation myocardial infarction.

Introduction

Insulin-like growth factor-1 (IGF-1) has anti-inflammatory and pro-repairing properties that make it antiatherogenic [1, 2]. Circulating IGF-1 is mainly released by the liver under the regulation of growth hormone and executes all of its physiological effects via binding to its receptor [2]. To date, several studies have already described the

importance of IGF-1 on atherosclerosis with its large biological effects and therapeutic potential. Although the results of these trials are inconclusive, in general, there is an inverse relation between IGF-1 levels and atherosclerosis [2, 3]. Insulin-like growth factor-1 reduces oxidative stress, inflammation and atherogenesis in the vasculature and plays a major role in vasodilatory responses by regulating nitric oxide (NO) production in the endothe-

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um [2]. No-reflow is an important complication of primary percutaneous coronary intervention (PPCI) with poor clinical outcomes, occurring more frequently in the setting of acute ST-elevation myocardial infarction (STEMI) [4]. The angiographic no-reflow phenomenon is defined as severely impaired forward coronary flow (Thrombolysis in Myocardial Infarction (TIMI) < 3) in the absence of residual stenosis, dissection or thrombosis [5–9]. Although the underlying mechanisms of no-reflow remain obscure, microvascular plugging, thrombotic debris, cellular edema, reperfusion injury, endothelial dysfunction, coronary vasospasm and microvascular spasm are likely to be closely related [4, 6, 7, 10]. The prevalence of no-reflow varies from 2% up to 50%, depending on the definition, recognition methods and selected patient population [6, 11]. Patients with no-reflow tend to experience more early post-infarction complications, heart failure, cardiogenic shock and death [4, 6, 10, 11]. According to our knowledge, there is no study investigating the interactions between IGF-1 levels and development of the no-reflow phenomenon in English literature.

Aim

Thus, we hypothesized that low levels of IGF-1 may be associated with the severity and extent of coronary artery disease (CAD) and development of the coronary no-reflow phenomenon in patients with acute ST-elevation myocardial infarction and investigated the role of the IGF-1 molecule in the coronary no-reflow phenomenon and severity of CAD in patients with acute STEMI in a tertiary hospital.

Material and methods

Study patients

This is an observational, case-control comparative study. Patients with STEMI who underwent PPCI within 90 min after first medical contact were included. A total of 113 patients were selected for enrollment in the trial. Forty-nine patients developed no-reflow (group 1). Sixty-four patients did not (group 2). All patients were given similar medical treatment according to related guideline directed medical treatment approaches except for no-reflow treatment. Exclusion criteria were cardiogenic shock, complete AV block on admission, rescue percutaneous coronary intervention (PCI), intervention on vein grafts, coronary dissection, angiographically visible distal embolization, severe heart failure, severe bronchospastic disease, patients with previous percutaneous revascularization and/or myocardial infarction, severe renal failure (creatinine > 3 mg) and liver failure. Diabetic patients on insulin therapy or poorly controlled diabetic patients (such as diabetic ketoacidosis and hyperosmolar nonketotic coma), patients with acromegaly or growth hormone deficiency, patients on steroid therapy and patients with known malignancy were also excluded.

All patients provided written informed consent and the study protocol was approved by the ethics committee of the hospital in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Insulin-like growth factor-1 measurement

Arterial blood (20 ml) was collected from the femoral artery sheath after completing primary percutaneous intervention. After the collection, the tubes were centrifuged at 3000 rpm for 10 min and the serum transferred to capped tubes for storage. All aliquots were anonymized and stored frozen at -40°C for 6 months until analyzed. All analyses were performed using Siemens Immulite IGF-I assay with solid-phase enzyme labeled chemiluminescent immunometric assay [12]. Hemolyzed, lipemic and icteric serums were not used for analysis. The result of the IGF1 test was given in ng/ml.

Coronary angiography

All angiograms were performed with 7 Fr guiding catheters without side holes at a speed of 30 frames per second. Coronary angiography was carried out by an automatic mechanical injector (ACIST CVi, Bracco Imaging S.p.A. Italy). All observations were performed by an interventional cardiologist who was blinded to the study groups. The TIMI flow score was defined by the degree of flow into the epicardial artery as follows: grade 0, complete absence of flow beyond the point of obstruction; grade 1, some contrast material flows distal to the obstruction but complete arterial visualization is not achieved; grade 2, delayed opacification of the entire artery; and grade 3, full prompt visualization of the entire artery [13].

Coronary artery disease scoring

The severity and extent of CAD were evaluated according to the Gensini score and Syntax score. Gensini score depends on the degree of the coronary artery stenosis and its geographic importance [14]. The degree of luminal narrowing, concentricity and eccentricity of the plaques are evaluated. 1 point is given for 1–25% stenosis, 2 points for 26–50%, 4 points for 51–75%, 8 points for 76–90%, 16 points for 91–99%, and 32 points for 100% stenosis. Further, each lesion's point is multiplied by the coefficient which is given for each principal vascular segment due to the functional significance (the left main coronary artery $\times 5$; the proximal segment of the left anterior descending coronary artery (LAD) $\times 2.5$; the proximal segment of the circumflex artery $\times 2.5$; the mid-segment of the LAD $\times 1.5$; the right coronary artery, the distal segment of the LAD, the posterolateral artery and the obtuse marginal artery $\times 1$; and others $\times 0.5$), and the sum of all gives the total score [14]. The Syntax score corresponding to the lesion complexity was measured by the coronary tree characteristics and the lesion locations

and specifics [15]. The score is measured using the openly accessible web based score calculator (<http://www.syntaxscore.com>). Scorings were performed and averaged by two observers who were blinded to the study groups.

Statistical analysis

Statistical calculations were performed with Number Cruncher Statistical System 2007 Statistical Software program for Windows (Utah, USA). Besides standard descriptive statistical calculations (mean and standard deviation, median, interquartile range), for the variables that showed a normal distribution, the unpaired *t* test was used in the comparison of groups, for the variables not having a normal distribution, the Mann-Whitney *U* test was used in the comparison of groups, and the χ^2 test was performed during the evaluation of qualitative

data. The Pearson correlation test was used to determine the relationships between the variables. The statistical significance level was established at $p < 0.05$.

Results

Patient and control groups were similar in terms of sex, age, body mass index, presence of diabetes and hypertension and family history of coronary artery disease. Patients' characteristics, differences and study results are presented in Table I. Although IGF-1 levels tend to be lower in no-reflow patients, results were not statistically different between the no-reflow group and the control group (116.65 ± 51.72 vs. 130.82 ± 48.76 , $p = 0.130$). In-hospital mortality was higher in the no-reflow group (8.77% vs. 0%, $p = 0.016$). Gensini and Syntax scores were lower in the control group. However, there was no correla-

Table I. Clinical, demographic and interventional characteristics of both groups

Parameter	No-reflow (n = 49)	Lack of no-reflow (n = 64)	Value of <i>p</i>
Age [years]	58.16 \pm 12.35	55.03 \pm 8.98	0.111
Sex, n (%)	Male	41 (83.67)	0.596
	Female	8 (16.33)	
BMI [kg/m ²]	28.13 \pm 4.13	27.75 \pm 4.98	0.732
Diabetes mellitus, n (%)	10 (20.41)	10 (15.63)	0.680
Hypertension, n (%)	15 (30.61)	20 (31.25)	0.942
Hyperlipidemia, n (%)	12 (24.49)	11 (17.19)	0.471
Alcohol use, n (%)	4 (8.16)	13 (20.31)	0.127
Smoking, n (%)	21 (42.86)	49 (76.56)	0.005
Family history of CAD, n (%)	19 (38.78)	31 (48.44)	0.404
In-hospital mortality, n (%)	5 (10.20)	0 (0.00)	0.031
IGF-1	116.65 \pm 51.72	130.82 \pm 48.76	0.130
Gensini score	67.4 \pm 26.85	47.13 \pm 24.8	0.0001
Syntax score	25.48 \pm 10.3	17.94 \pm 8.03	0.0001
Number of stents	1.45 \pm 0.71	1.16 \pm 0.6	0.019
Stent diameter	3.33 \pm 0.47	2.98 \pm 0.86	0.013
Stent length	30.04 \pm 16.14	23.5 \pm 12.13	0.015
Glucose	177.16 \pm 94.42	144.87 \pm 74.78	0.041
Total cholesterol	193.73 \pm 37.53	204.24 \pm 48.3	0.204
Triglyceride	109.87 \pm 61.58	151.52 \pm 87.44	0.005
LDL	126.61 \pm 33.59	141.43 \pm 42.72	0.044
HDL	45.93 \pm 12.43	39.66 \pm 9.78	0.004
Creatinine	0.93 \pm 0.32	0.84 \pm 0.17	0.04
Troponin max.	16.02 \pm 14.95	6.52 \pm 8.04	0.0001
EF	41.5 \pm 9.75	51.05 \pm 8.84	0.0001
RDW	13.3 \pm 1.08	13.1 \pm 1	0.301
Platelet count	248.05 \pm 61.81	258.19 \pm 56.09	0.350
MPV	8.21 \pm 0.86	8.47 \pm 0.83	0.096
Neutrophil count	10325.18 \pm 3950.56	8754.76 \pm 3428.08	0.022
Lymphocyte count	1681.25 \pm 1027.61	2150.08 \pm 914.42	0.01
NLR	8.57 \pm 7.25	5.29 \pm 3.94	0.002

tion between Gensini and Syntax scores and IGF-1 levels ($r = -0.071$, $r = 0.479$, $r = -0.158$, $p = 0.113$ respectively). Interestingly, current smoking was higher in the control group than in the no-reflow group. The number, length and diameter of stents used were lower in the control group. On admission, serum creatinine and blood glucose levels were lower in the control group. Serum low density lipoprotein (LDL) and triglyceride levels were higher in the control group. Initial troponin levels were not statistically different between the groups (5.41 ± 7.78 vs. 3.14 ± 6.46 , $p = 0.086$). Peak troponin levels were significantly higher in the no-reflow group than in the control group (16.02 ± 14.95 vs. 6.52 ± 8.04 , $p = 0.0001$). Neutrophil count and neutrophil to lymphocyte ratio (NLR) were higher in the no-reflow group (8754.76 ± 3428.08 vs. 10325.18 ± 3950.56 and 5.29 ± 3.94 vs. 8.57 ± 7.25 , $p = 0.02$, $p = 0.002$ respectively). There was no difference between the groups in platelet count or mean platelet volume ($p = 0.350$ and $p = 0.096$ respectively).

Discussion

In this study, the no-reflow or slow flow phenomenon was mostly seen in patients who have more diffuse and severe coronary artery disease, with higher Gensini and Syntax scores. The major finding of this study was that IGF-1 levels were not different between the no-reflow group and the control group. Thus, there was no association between the no-reflow phenomenon and IGF-1 levels. There was also no association between Gensini and Syntax scores and IGF-1 levels. Previously published studies have already demonstrated the effect of IGF-1 on vascular homeostasis [2, 3, 16]. Nitric oxide plays an important role in the regulation of endothelial function due to its potent vasodilator effect and sensitivity of redox status of the endothelium [2]. Increasing evidence indicates that IGF-1 preserves endothelial function and plays a major role in vasodilatory responses by increasing NO production and decreasing oxidative stress and attenuating endothelin-1 induced contractile responses in the vascular endothelium [2]. Endothelial dysfunction, coronary vasospasm and microvascular spasm may play a role in the pathogenesis of the no-reflow phenomenon. Although IGF-1 levels tended to be lower in no-reflow patients in our study, there was no statistically significant association between development of the no-reflow phenomenon and IGF-1, which has potential vasodilator effects on vascular function. Although microvascular dysfunction is one of the possible pathophysiological mechanisms for the no-reflow phenomenon [4, 6, 7, 10], thrombus burden and atherosclerotic debris burden may play a more effective role in development of the no-reflow or slow flow phenomenon. According to the results of our study, IGF-1 may not have significant contribution to the development of no-reflow or slow flow in patients with STEMI. Insulin-like growth factor-1 also has positive effects on the development of

cardiac structures, myocardial contraction, heart beats and ejection fraction and increases cardiac performance and decreases wall tension [17]. Animal studies have shown that IGF-1 has the ability to reduce the atherosclerotic burden by its pleiotropic, antioxidant and antiinflammatory effects [1, 2]. Low IGF-1 expression and/or bioavailability may play a role in oxidized LDL induced cytotoxicity and apoptosis in vascular smooth muscle cells that help plaque destabilization and rupture [3]. High IGF-1, with its receptor and binding proteins, may protect the atherosclerotic plaque against destabilization and rupture [16]. The receptor of IGF-1 creates a hybrid receptor with the insulin receptor, resulting in more IGF-1 expression, which makes vascular smooth muscle cells insensitive to insulin [2]. Low levels of IGF-1 are associated with chronic insulin resistance and impaired glucose tolerance [16, 18]. Insulin-like growth factor-1 levels are also lower in patients with poorly controlled diabetes [1]. According to several studies, IGF-1 levels are correlated with cardiovascular disease risk in the general population [16]. It has been reported that low levels of IGF-1 may be an independent risk factor for myocardial infarction, coronary artery disease and increased carotid intima-media thickness, and interfere with obesity, insulin resistance, impaired glucose intolerance and left ventricular hypertrophy [18]. However, clinical studies have produced conflicting results regarding the relation between IGF-1 and different forms of CAD [1, 18–20]. Spallarossa *et al.* observed decreased IGF-1 levels in patients with advanced CAD [21]. Burchardt *et al.* determined higher IGF-1 levels in patients with advanced CAD than patients with hemodynamically insignificant CAD [16]. They stated that high IGF-1 levels are a physiological regulatory mechanism against CAD. Patients with high IGF-1 levels experience more stable angina than acute coronary syndromes [22]. Ruotolo *et al.* demonstrated an independent association between IGF-1 levels and progression of CAD in young male survivors of MI [23]. However, Botker *et al.* could not show an association between IGF-1 levels and CAD [24]. Similarly, Lawlor *et al.* could not show any association between IGF-1 levels and coronary artery disease [25]. In our study, there was no association between IGF-1 levels and the extent and severity of CAD. There was no association between the no-reflow phenomenon and IGF-1 levels, also, despite the reports asserting that IGF-1 plays an important role in arterial vasodilatation by controlling endothelial NO production and reduces inflammation and oxidative stress [2, 17]. Changes in lipid profile after acute coronary syndrome have been known for at least 50 years [26]. While total cholesterol, LDL and HDL levels tend to decrease by 0–20%, triglyceride levels increase by 20–30% [26, 27]. Stress-induced myocardial damage alerts adrenergic activation associated lipolysis and mobilizes free fatty acids [26, 27]. Likewise, LDL levels were lower in patients with no-reflow than controls in our study. Higher creatinine levels detected in the no-reflow group may be associated with

impaired coronary flow. Interestingly, current smokers had the no-reflow phenomenon less often in our study. According to our study, neutrophil count and NLR may also predict no-reflow, which may be explained by an excessive inflammatory response in no-reflow patients. The NLR index is known to specify the inflammatory status [28]. The NLR has recently been shown as a predictor of mortality in patients with acute myocardial infarction, stable patients with CAD and in patients undergoing PCI and all other conditions [28, 29]. In-hospital mortality was higher in the no-reflow group, who have higher levels of neutrophil counts and NLR in this study. The number, length and diameter of stents used were higher in no-reflow patients, also.

Study limitations: Since this was a single-center study limited to PPCI of native vessels, the number of patients was small, representing the major limitation. Another limitation of our study is that unfortunately we do not have enough sound data about balloon inflation pressures and patients' previous medications. Another issue is the high frequency of the no-reflow phenomenon in our study population, approximately 50% of all patients. It is high as compared to data of other large scale studies, even on STEMI patients only [30]. This may be related to the methodology of evaluation and definition of no-reflow. Since the no-reflow group included patients with higher Gensini and Syntax scores, the slower flow might be related to some residual stenoses within the infarct-related artery. Unfortunately, we were not able to use thrombus aspiration catheters during the study period; manual thrombus aspiration might have changed our results. In the CathPCI Registry, Harrison *et al.* reported that older age, STEMI, prolonged interval from symptom onset to intervention, cardiogenic shock, longer lesion length, higher risk class C lesions, bifurcation lesions, and periprocedural TIMI flow grade were clinical and angiographic variables independently associated with development of the no-reflow phenomenon [30]. Since the no-reflow phenomenon was blindly evaluated, possible differences do not change the value of results. However, large scale multicenter studies may reveal different results.

Conclusions

In this study, although no-reflow or slow flow was mostly seen in patients with more diffuse and severe CAD, there was no association between development of the no-reflow phenomenon and the severity of CAD or IGF-1 levels. However, large scale studies are needed to verify these results.

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