

## ORIGINAL ARTICLE

# No-reflow phenomenon predictors after primary PCI in STEMI patients

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**Aim:** Study of no-reflow phenomenon (NRP) in patients (pts) with STEMI and primary percutaneous coronary intervention (PCI) in relation with age, gender, cardiovascular risk factors, prothrombotic comorbidities (PC), STEMI location on ECG, coronary artery implicated in STEMI, characteristics of obstructive lesion. **Method:** 131 pts with STEMI, TIMI 3 coronary flow after PCI, were assessed 7 days after primary PCI for NRP using transthoracic Doppler echocardiography (TTDE) of coronary flow velocity [31 men (M) <40 years (24%); 7 women (W) <40 years (5%) not included in statistical analysis; 70M >40 years (53%) and 23 W >40 years (18%)]. Statistics in SPSS 20 with comparisons between groups, correlations and logistic regression;  $p < 0.05$  statistically significant. **Results:** NRP diagnosed in 36 pts (27%) was significantly more frequent in M <40 years vs M >40 years ( $p = 0.04$ ), W >40 years vs M >40 years ( $p = 0.02$ ) and was correlated with anterior STEMI [ $p = 0.03$ ,  $p < 0.001$ ,  $p = 0.04$ ], LAD occlusion [ $p = 0.03$ ,  $p < 0.001$ ,  $p = 0.009$ ], coronary obstruction by thrombus in M <40 years ( $p < 0.001$ ) and atherosclerotic plaque in M >40 years ( $p = 0.04$ ). NRP was independently associated with PC [ $p = 0.04$ ,  $p = 0.01$ ], hypertension in M <40 years ( $p = 0.009$ ), dyslipidemia in M >40 years ( $p = 0.003$ ), diabetes and smoking in W >40 years [ $p = 0.04$ ,  $p = 0.03$ ]. **Conclusions:** No-reflow phenomenon, diagnosed using TTDE coronary flow parameters, occurring in 27% STEMI patients after primary PCI, was positively correlated with LAD obstruction, anterior STEMI, occlusion by thrombus in men under 40 years and atherosclerotic plaque in those over 40 years. The intervention of cardiovascular risk factors seems to be modulated by age and gender.

**Keywords:** “no-reflow” phenomenon, primary PCI in STEMI, Doppler echocardiography of coronary arteries

**Scop:** Studiul fenomenului no-reflow (FNR), la pacienți (pts) cu STEMI și revascularizare coronariană percutanată (PCI) primară, în relație cu vârsta, sexul, factorii de risc cardiovascular, comorbiditățile protrombotice (CP), localizarea ECG a STEMI, artera coronară implicată în infarct, caracteristicile leziunii obstructive. **Metoda:** 131 (pts) cu STEMI, flux coronarian TIMI3 după PCI, au fost evaluați la 7 zile după PCI pentru FNR diagnosticat prin viteza fluxului coronarian măsurată prin ecocardiografie Doppler transtoracică (TTDE). [31 bărbați (B) <40 ani (24%); 7 femei (F) <40 ani (5%), neincluse în analiza statistică; 70B >40 ani (53%) și 23F >40 ani (18%)]. Statistică în SPSS 20, comparații între grupuri, corelații și regresie logistică;  $p < 0,05$  statistic semnificativ. **Rezultate:** FNR diagnosticat la 36 pts (27%), a fost semnificativ mai frecvent la B <40 ani vs B >40 ani ( $p = 0,04$ ), F >40 ani vs B >40 ani ( $p = 0,02$ ) și corelat cu localizarea anterioară STEMI [ $p = 0,03$ ,  $p < 0,001$ ,  $p = 0,04$ ], ocluzia ADA [ $p = 0,03$ ,  $p < 0,001$ ,  $p = 0,009$ ], obstrucția prin tromb la B <40 ani ( $p < 0,001$ ) și placă aterosclerotică la B >40 ani ( $p = 0,04$ ). FNR s-a asociat independent cu CP [ $p = 0,04$ ,  $p = 0,01$ ], hipertensiunea la B <40 ani ( $p = 0,009$ ), dislipidemia la B >40 ani ( $p = 0,003$ ), diabetul și fumatul la F >40 ani [ $p = 0,04$ ,  $p = 0,03$ ]. **Concluzii:** Fenomenul no-reflow diagnosticat prin parametrii fluxului coronarian evaluat prin TTDE la 27% pacienți cu STEMI după PCI primar, s-a corelat cu obstrucția ADA, STEMI anterior, ocluzia prin tromb la bărbații sub 40 ani și placă aterosclerotică la cei peste 40 de ani. Intervenția factorilor de risc cardiovascular apare modulată de vârstă și sex.

**Keywords:** “no-reflow” phenomenon, primary PCI in STEMI, Doppler echocardiography of coronary arteries

## INTRODUCTION

The no-reflow phenomenon after interventional or pharmacological reperfusion in acute myocardial infarction, a phenomenon variably defined over time, occurs in the absence of the mechanical obstruction of

the epicardial artery involved in infarction through the deficit of perfusion at microcirculation level explaining the post-reperfusion myocytic lesion<sup>1-5</sup>.

In ST-segment elevation myocardial infarction (STEMI), the persistence of the no-reflow phenome-

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non is involved in the evolution of the myocyte lesion to myocyte death with increase of the infarcted area and of the risk of major cardiovascular events<sup>6,7</sup>. After myocardial infarction, the no-reflow phenomenon is associated with an increased incidence of heart failure, arrhythmias, death on short, medium and long term<sup>6</sup> and it is an independent predictor of mortality at 5 years<sup>8</sup>. The no-reflow phenomenon thus minimizes in STEMI patients the benefits of epicardial coronary artery recanalization obtained by primary angioplasty. Clinical studies that assessed the no-reflow phenomenon dynamics reported its reversibility with favourable prognostic impact at 1-6 and 12 months post infarction, by reducing 5-6 times the risk of death<sup>6</sup>. Identification of risk factors of the no-reflow phenomenon, its prophylaxis and therapy seem to be important goals of interventional reperfusion, which has to be extended from opening the coronary artery involved in the infarction to the optimization of the myocardial perfusion by obtaining and maintaining perfusion at microcirculation level<sup>9</sup>.

The diagnosis of the no-reflow phenomenon after STEMI is a challenge in clinical practice and can be done after percutaneous coronary angioplasty (PCI), in the presence of the TIMI3 flow (Thrombolysis In Myocardial Infarction)<sup>13</sup>, through a coronary angiogram assessment of „TIMI frame count”<sup>11,11</sup> and of the myocardial BLUSH grades (MBG)<sup>12</sup>, by assessing on the electrocardiogram (ECG) the reduction of the ST segment elevation after PCI<sup>14,15</sup>, by determining the coronary flow reserve using the intracoronary Doppler ultrasound and by evaluating the microvascular perfusion distribution via an intracoronary contrast echocardiography<sup>16,17</sup>. The non-invasive assessment of the no-reflow phenomenon with gadolinium-based magnetic resonance and positron emission tomography, evaluating the microvascular lesions and the infarction extension is expensive and has limited availability in clinical practice<sup>5,18,19</sup>. In this context, the diagnosis of the no-reflow phenomenon in patients with STEMI and primary PCI using the transthoracic Doppler echocardiography (TTDE) evaluation of the flow in the coronary artery involved in the infarction and the coronary flow reserve is easier, with a sensitivity and specificity substantially the same with the invasive methods<sup>19,20</sup>, especially in assessing the no-reflow phenomenon in left anterior descending coronary artery (LAD), with fewer studies for left circumflex coronary artery (LCX) and right coronary artery (RCA) that occur with increasing technical performance in echocardiography<sup>5,21-25</sup>.

## AIM OF THE STUDY

Evaluation of risk factors of the no-reflow phenomenon in STEMI patients revascularized by primary coronary intervention, the no-reflow phenomenon being assessed by transthoracic Doppler echocardiography by determining the parameters of the flow in the coronary artery involved in the infarction.

## MATERIAL AND METHOD

Prospective study of 131 patients with STEMI, who did not show on admission any electrocardiographic signs of necrosis, revascularized by primary percutaneous coronary intervention (PCI), performed in the Cardiology Clinic – Department of Interventional Cardiology of the County Clinical Emergency Hospital Braşov (SCJUBv) and in the Department of Interventional Cardiology of the Clinico Hospital Braşov during 2010-2014. The patients were evaluated by clinical examination, resting ECG, transthoracic Doppler echocardiography (TTDE) and biological tests that included the serum levels of CK, CK-MB or TnT.

Clinical data recorded demographic parameters, cardiovascular risk factors, prothrombotic comorbidities such as concomitant acute infections, chronic inflammatory diseases (systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease), haematological diseases (thrombocytopenia) and documented history of ischemic heart disease.

The STEMI diagnosis was made in the presence of chest pain of ischemic nature and ST-segment elevation on the ECG performed at the Emergency Room of the County Clinical Emergency Hospital Braşov (SCJUBv), according to the diagnostic criteria presented in the “Universal definition of myocardial infarction”<sup>28</sup> and “Third universal definition of myocardial infarction”<sup>29</sup>. Serum levels of CK, CK-MB and TnT were determined in venous blood samples by spectrophotometry for CK, immunoassay for CK-MB and TnT on a Cobas 6000 device and its modules supported the diagnosis of values compliant with those generally recommended in the “Universal definition of myocardial infarction”<sup>28</sup>.

Cardiovascular risk factors were listed under the “ESC/EAS Guidelines for the management of dyslipidemia”<sup>30</sup>, European Guidelines on cardiovascular disease prevention in clinical practice<sup>31</sup>, and “Guidelines for the management of arterial hypertension”<sup>32</sup>. Arterial hypertension was considered starting with values >140/90 mmHg, obesity from BMI  $\geq 30$  kg/m<sup>2</sup>, dyslipidemia from LDL cholesterol levels >100 mg/dL.

Resting ECG recorded 12 usual leads, right and posterior leads and was performed before and after PCI and 90 minutes after PCI on a Nihon Kohden Ecg-9022 device.

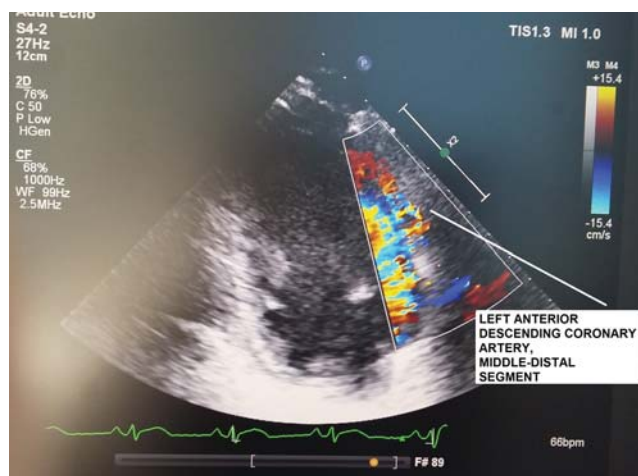
Serum level of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose and creatinine were measured by standard enzymatic methods on a Cobas 6000 analyzer.

Coronary angiography was performed with a Philips Allura FD 10 cardiovascular X-ray system in the Interventional Cardiology Department of SCJUBv and a Siemens Artis Zee Floor in the Interventional Cardiology Department of Clinicco Hospital Braşov.

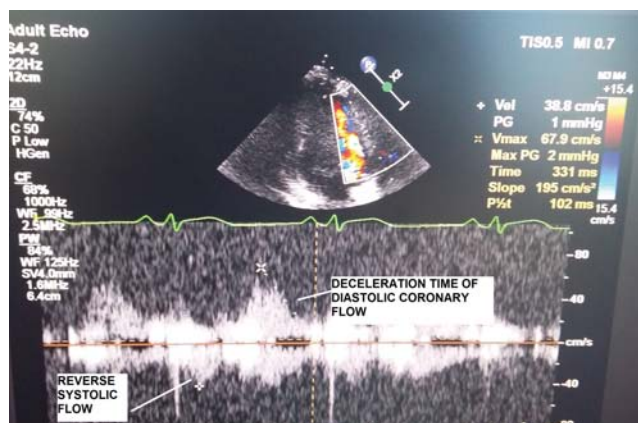
Interventional revascularization was performed after an average time of 6.22 hours (1-72 hours) after the onset of ischemic pain by angioplasty and BMS stent implantation in 125 patients and thromboaspiration without stent in 6 patients. No protective devices of distal coronary embolization was used. Periprocedural treatment was started in the Emergency Room of SCJUBv or prehospital with acetylsalicylic acid 250 mg and clopidogrel 300 mg or 600 mg. High molecular weight heparin 100 U/kg was administered intraprocedural also depending on the evolution of the TIMI-MBG score: eptifibatide iv, intracoronary thrombolysis, intracoronary nitroglycerin.

At coronarography were assessed: the involved coronary artery and imaging characteristics of the obstructive lesion, lesions of other coronary arteries, TIMI flow grades before and after PCI, myocardial BLUSH grades (MBH) after PCI. Angiograms of coronary vessels were interpreted by two cardiologists of the interventional department, who participated in performing the interventional procedure.

The no-reflow phenomenon was assessed by the flow parameters of the coronary artery involved in infarction, using Doppler transthoracic echocardiography (TTE), performed with Philips Sonos 7500 and Philips Affiniti 50G ultrasound systems on the seventh day after PCI in patients with TIMI 3 post intervention flow, in order to analyse the perfusion deficit in the coronary microcirculation that explains the post-reperfusion myocytic lesion<sup>1-5</sup>. The seventh day after PCI was chosen to assess the no-reflow phenomenon, when its reversibility decreases, an aspect with subsequent prognostic impact<sup>6,7</sup>. Although the no-reflow phenomenon reflects a deficitary coronary microvascular perfusion, under conditions of epicardial flow restored after PCI in STEMI, TTE this is reflected in the epicardial artery by modification of flow parameters (described below),



**Figure 1.** TTDE - Colour Doppler: Left anterior descending coronary artery, middle-distal segment.



**Figure 2.** TTDE - PW: Coronary flow with no-reflow velocity pattern.

which is presented in angiography as TIMI 3 with Blush 0/I<sup>15,21,23,25,27,33</sup>.

The transducer was used in the 3.5-5 MHz “second harmonic” frequency band for two-dimensional evaluation and 2-2.5 MHz for colour Doppler and pulse (PW) examination<sup>23,25,26</sup>.

The sections used for transthoracic echocardiography (TTE) viewing of the coronary arteries, sections frequently modified (mode) compared to the standard one, were (according to Marek Krzanowski, Wojciech Bodzoń and Paweł Petkow Dimitrow, Cardiovascular Ultrasound 2003)<sup>23</sup> for Left Main Coronary Artery (LMCA) / proximal Left Anterior Descending Coronary Artery (LAD): modified (mod.) parasternal short axis view (PSAX), mod. Parasternal long axis view (PLAX), mod. apical 5 chamber view (AP5C), mod. apical 3 chamber (AP3C) view, mod. subcostal long axis (SUB-LAX) view; for middle LAD: mod. PSAX view, mod. PLAX view, mod. AP5C view, mod. AP3C view,



mod. SUB-LAX view; for distal LAD: AP3C view, mod. AP5C view; for proximal Left Circumflex Coronary Artery (LCX): mod. PSAX view, mod. PLAX view, mod. AP5C view; for middle LCX: mod. PSAX view, mod. PLAX view, mod. AP5C view; for distal LCX there are no well-standardized sections; for proximal Right Coronary Artery (RCA): mod. PSAX view, mod. PLAX view, mod. AP5C view; for middle RCA : mod. subcostal short axis (SUB-SAX) view; for distal RCA (Right Posterior Descending Artery (RPD)): mod. apical 4 chamber (AP4C) view, mod. apical 2 chamber (AP2C) view, mod. SUB-LAX view<sup>23</sup>.

The transducer was used, according to other studies<sup>23</sup>, both at high frequencies, which provide an increased resolution for the two-dimensional mode and improves the sensitivity of the colour Doppler and PW examination, and at low frequencies, which provide a good penetration with higher Nyquist limits for the colour Doppler and PW examinations, to the detriment of a lower resolution and of a lower Doppler sensitivity<sup>23</sup>. Likewise, high frequencies were used for viewing apical structures, as well as distal LAD and low frequencies for RCA, LCX, proximal and middle LAD<sup>23</sup>. Use of the „harmonic” option for the two-dimensional mode has improved the quality of images<sup>23,26</sup>. The Nyquist limit used for colour Doppler was between 0.1-0.4m/s, reducing the area of the colour window to a minimum<sup>23,26</sup>. Doppler PW examination was performed at an angle of less than 60°, with sample width of about 3 mm<sup>23</sup>. Nyquist limit for PW was 0.15-0.25 m/s<sup>25,26</sup>.

Normal coronary flow that can be highlighted through TTDE in the LAD, LCX, RCA and branches of coronary arteries show a biphasic, systolic and diastolic appearance that prevails, with velocities oriented in the same direction, for which measurements of speed, time of diastolic deceleration, velocity-time integrals, etc. can be performed<sup>23-27</sup>.

TTDE diagnostic parameters for the no-reflow phenomenon, coronary flow (Figure 1,2), studied in literature especially at LAD level and less at LCX and RCA level, were: systolic velocity reverse  $\geq 10$  cm/s and duration  $\geq 60$  ms and diastolic deceleration time  $< 600$  ms<sup>5,21,23,25,27,33</sup>.

Four groups were formed by age and gender: 31 men under 40 years old (24%) (M <40 years), 7 women under 40 years (5%) (F <40 years), 70 men over 40 years (53%) (M >40 years), 23 women over 40 years (18%) (F >40 years). The age of 40 years was chosen for distribution on subgroups given that myocardial

infarction before 40 years of age is described as myocardial infarction of young people, with peculiarities of etiology, morphology of the coronary obstructive lesion, complications and prognosis<sup>34</sup>.

The no-reflow phenomenon was analysed in relation to age, gender, cardiovascular risk factors, prothrombotic comorbidities, previously documented ischemic heart disease, STEMI location, coronary artery involved in infarction and coronary angiography characteristics of the obstructive lesion.

## STATISTICAL ANALYSIS

Statistical analysis used the IBM SPSS Statistics 20 program. Continuous variables with normal distribution were expressed as mean values and standard deviation, and categorical and ordinal variables were expressed as frequencies and percentages. Differences between two groups were assessed by the nonparametric Mann-Whitney U test, and between 3 or more groups by the Kruskal-Wallis test. Correlations between the no-reflow phenomenon and various parameters were performed using Spearman bivariate correlation. Independent predictors of the no-reflow phenomenon were determined by multivariate logistic regression. The level of statistical significance was set at  $p < 0.05$ .

## RESULTS

Average age of STEMI patients was  $49.47 \pm 14.23$  years (21–86 years). In patients under 40 years of age, the average age of men was similar to that of women [ $(35.97 \pm 4.51)$  years vs  $(38.14 \pm 3.29)$  years] and in patients over 40 years of age, the average age of men was significantly lower than the age of women [ $(50.57 \pm 11.49)$  years vs  $(67.78 \pm 9.99)$  years], ( $p < 0.001$ ).

The average time from the onset of the first pain of ischemic nature until the performance of the primary angioplasty was of 6.22 hours in the entire group of patients, noticeably equal for men and women under 40 years and significantly higher in women over 40 years compared to the men of the same age group ( $p = 0.002$ ) (Table 1) and in men over 40 years compared to those under 40 years ( $p = 0.002$ ).

The frequency of arterial hypertension was significantly higher in men compared to women under 40 years and noticeably equal for men and women over 40 years. Diabetes mellitus significantly more frequent in women over 40 years was noticeably equal in terms of frequency in men and women under 40 years. The frequency of dyslipidemia and smoking did not vary sig-

**Table 1. Characteristic of STEMI patients**

	<b>Pts.&lt;40 years (n=38)</b>	<b>Pts.&gt;40 years (n=93)</b>	<b>p</b>	<b>M&lt;40 years (n=31)</b>	<b>F&lt;40 years (n=7)</b>	<b>p</b>	<b>M&gt;40 years (n=70)</b>	<b>F&gt;40 years (n=23)</b>	<b>p</b>
Age (years)	36.36 +/- 4.35	54.82 +/- 13.36	<0.001	35.97 +/- 4.51	38.14 +/- 3.29	ns	50.57 +/- 11.49	67.78 +/- 9.99	<0.001
Time symptom-PCI	3.56 +/- 3.46	7.31 +/- 9.26	<0.001	3.77	2.57	ns	6.58	9.52	0.002
Average no. of CV risk factors	1.7 +/- 1.02	2.6 +/- 1.39	0.001	1.8 +/- 1.02	1.2 +/- 0.89	ns	2.4 +/- 1.41	3.4 +/- 1.07	0.005
Arterial hypertension	23(61%)	68(73%)	ns	22(70%)	1(14%)	0.006	48(68%)	20(86%)	ns
Diabetes mellitus	2 (6%)	22(24%)	0.014	2 (6%)	0(0%)	ns	13(18%)	9(39%)	0.045
Dyslipidemia	14 (37%)	58(62%)	0.008	11(35%)	3(42%)	ns	41(58%)	17(73%)	ns
Smoking	16 (42%)	41(44%)	ns	13(41%)	3(42%)	ns	33(47%)	8(34%)	ns
Obesity	8 (21%)	20(22%)	ns	7(22%)	1(14%)	ns	11(15%)	9(39%)	0.018
Prothrombotic comorbidities	11 (29%)	21(23%)	ns	6(19%)	5(71%)	0.007	9(12%)	12(52%)	<0.001
IHD	5 (14%)	37(40%)	0.003	5(16%)	0(0%)	ns	21(30%)	16(69%)	0.001
Anterior STEMI	23 (60%)	40(43%)	ns	19(63%)	4(57%)	ns	28(40%)	12(52%)	ns
Anterolateral STEMI	4 (11%)	4(5%)	ns	3(9%)	1(14%)	ns	3(5%)	1(4%)	ns
Inferior STEMI	8 (21%)	15(16%)	ns	6(20%)	2(29%)	ns	10(14%)	5(22%)	ns
Inferior STEMI +RV	3 (8%)	34(36%)	0.001	3 (8%)	0(0%)	ns	29(41%)	5(22%)	ns
Anterior STEMI (cumulative)	27(71%)	44(48%)	0.014	22(71%)	5(71%)	ns	31(44%)	13(56%)	ns
Inferior STEMI (cumulative)	11 (29%)	49(53%)	0.014	9(29%)	2(29%)	ns	39(56%)	10(44%)	ns
Multi-vessel coronary impairment	1.94	2.48	<0.001	2.25	0.57	0.002	2.45	2.56	ns
LAD occlusion	27 (71%)	39(42%)	0.003	22(71%)	5(72%)	ns	27(39%)	12(52%)	ns
LCX occlusion	2 (6%)	15(16%)	ns	1(3%)	1(14%)	ns	12(17%)	3(13%)	ns
RCA occlusion	9 (24%)	34(36%)	ns	8(26%)	1(14%)	ns	26(37%)	8(35%)	ns
IB occlusion	0 (0%)	3(4%)	ns	0(0%)	0(0%)	ns	3(4%)	0(0%)	ns
LMCA occlusion	0 (0%)	2(3%)	ns	0(0%)	0(0%)	ns	2(3%)	0(0%)	ns
Obstructive thrombus	21(56%)	17(18%)	<0.001	16(51%)	5(71%)	ns	15(21%)	2(9%)	ns
Obstruction by thrombus on ats plaque	10 (26%)	50(54%)	0.004	8(26%)	2(29%)	ns	34(49%)	16(69%)	ns
Obstruction by ats plaque	7 (18%)	26(28%)	ns	7(23%)	0 (0%)	ns	21(30%)	5(22%)	ns
NRP	12 (31.6%)	24 (25.8%)	ns	12 (38.7%)	0 (0%)	0.05	14 (20%)	10 (43.4%)	0.026
pre-PCI thromboaspiration	23(61%)	48(52%)	ns	17(55%)	6(86%)	ns	32(46%)	16(69%)	0.048
Blush I	10 (26%)	19(20%)	ns	10(32%)	0(0%)	ns	13(18%)	6(26%)	ns
ECG necrosis post-PCI	12 (31%)	34(37%)	ns	12(38%)	0(0%)	0.023	22(31%)	13(54%)	0.028
↓ ST elevation <30%	7(19%)	21(22%)	ns	7(22%)	0(0%)	ns	14(20%)	7(30%)	ns
↓ ST elevation 30%-70%	14(37%)	33(36%)	ns	14(45%)	0(0%)	0.027	25(35%)	8(34%)	ns
↓ ST elevation >70%	17(44%)	39(42%)	ns	10(32%)	7(100%)	0.001	31(44%)	8(34%)	ns
↓ LVEF post-PCI	6(14%)	15(16%)	ns	6(17%)	0(0%)	ns	11(15%)	4(15%)	ns

Pts=patients; IHD=ischemic heart disease, LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; RCA=right coronary artery; IB=intermediate branch; LMCA=left main coronary artery; NRP = no-reflow phenomenon, ats = atherosclerotic; ns=not significant, anterior STEMI cumulative=anterior + anterolateral, inferior STEMI cumulative=inferior + inferior and RV, LVEF=left ventricular ejection fraction; Data are expressed in absolute and percentage frequency; mean and standard deviation

nificantly in men and women in the two age subgroups, the dyslipidemia being significantly more frequent in patients over 40 years compared to those under 40 years. Previously diagnosed ischemic heart disease (IHD) was recorded significantly more frequent in women over 40 years compared to men in both age subgroups ( $p=0.001$ ). Prothrombotic favourable conditions were significantly more frequent in women compared to men in both age subgroups (Table 1).

Myocardial infarction was considered anterior and anterolateral, if the ST-segment elevation appeared in anterolateral leads, inferior to the right ventricle, if the

ST-segment elevation appeared in the inferior-lateral-posterior leads or in the right precordial leads. There were no significant differences of the anterior or inferior location of STEMI between men and women of the two age subgroups (Table 1).

Coronary angiography revealed a more frequent involvement of LAD in STEMI in patients under 40 years and RCA in patients over 40 years (Table 1). Thrombotic obstruction of the coronary artery involved in STEMI has been reported in >1/2 of patients under 40 years, significantly more frequent among them compared to patients over 40 years, with no differences

**Table 2. Correlation of the no-reflow phenomenon with various parameters**

	M <40 years	M >40 years	F >40 years
Age (years)	0.039	ns	ns
Time symptom-PCI	ns	ns	ns
Average no. of CV risk factors	ns	ns	ns
Arterial hypertension	<0.001	ns	ns
Diabetes mellitus	ns	ns	ns
Dyslipidemia	ns	0.003	ns
Smoking	ns	ns	ns
Obesity	ns	ns	ns
Prothrombotic comorbidities	0.006	ns	ns
Previously diagnosed IHD	ns	0.042	0.001
Anterior STEMI	0.031	<0.001	0.009
Anterolateral STEMI	ns	ns	ns
Inferior STEMI	ns	ns	ns
Inferior STEMI and RV	ns	ns	ns
Anterior STEMI (cumulative)	0.037	<0.001	0.048
Inferior STEMI (cumulative)	ns	ns	ns
Multi-vessel coronary impairment	ns	0.05	ns
LAD occlusion	0.037	<0.001	0.009
LCX occlusion	ns	ns	ns
RCA occlusion	ns	ns	ns
IB occlusion	-	ns	-
LMCA occlusion	-	ns	-
Obstructive thrombus	<0.001	ns	ns
Obstruction by thrombus on atherosclerotic plaque	ns	ns	ns
Atherosclerotic plaque	ns	0.042	ns
pre-PCI thromboaspiration	ns	ns	ns
BLUSH I	<0.001	<0.001	<0.001
ECG necrosis post-PCI	<0.001	<0.001	<0.001
↓ ST elevation <30%	<0.001	<0.001	<0.001
↓ ST elevation 30%-70%	ns	ns	ns
↓ ST elevation >70%	neg 0.001	neg <0.001	neg <0.001
↓ FEVS post-PCI	<0.001	<0.001	0.047

IHD= ischemic heart disease, LAD= left anterior descending coronary artery; LCX= circumflex coronary artery; RCA= right coronary artery; IB=intermediate branch; LMCA=left main coronary artery, LVEF=left ventricular ejection fraction. Statistical analysis by: Spearman's bivariate correlations

between men and women of the two age subgroups. Obstruction by a thrombus on atherosclerotic plaque was found in approximately 1/3 of patients under 40 years and in >1/2 of those over 40 years, being significantly more frequent in women over 40 years compared to men under 40 years and in men over 40 years compared to those under 40 years. Coronary obstruction predominantly caused by atherosclerotic plaque was identified in approximately 1/4 of patients, in a noticeably equal proportion between men under 40 years and women and men over 40 years, this type of lesion has not been reported in women under 40 years (Table 1).

The frequency of the no-reflow phenomenon diagnosed by TTDE in the coronary artery involved in STEMI was: 27.5% in the whole group of patients with STEMI and revascularization by primary PCI, 43.4% in women over 40 years, 38.7% in men under 40 years and 20% in men over 40 years. The no-reflow pheno-

menon was significantly more common in men under 40 as compared to those over 40, and in women over 40 years compared to men over 40 years. The study of the correlation between the no-reflow phenomenon and the artery involved in infarction showed that it was significantly positively correlated with the anterior location of STEMI and obstruction of LAD, both in men under 40 years and in men and women over 40 years (Table 2).

The no-reflow phenomenon was positively correlated in men over 40 years with the presence of dyslipidemia, previously documented ischemic heart disease, multivessel affection and obstruction predominantly by atherosclerotic plaque of the coronary artery involved in infarction (Table 2). In men under 40 years there has been a positive correlation of the no-reflow phenomenon with arterial hypertension, prothrombotic comorbidities and obstruction by thrombus of the coronary artery involved in infarction, and in women

**Table 3. Independent predictors of the no-reflow phenomenon**

	M <40 years				p	M >40 years				p	F >40 years			
	p	OR	95% CI			OR	95% CI				OR	95% CI		
Arterial hypertension	0.009	8.51	1.69	42.74	0.408	0.71	0.32	1.58	0.819	0.78	0.09	6.20		
Diabetes mellitus	0.211	3.54	0.48	25.83	0.755	0.85	0.33	2.23	0.045	7.65	1.04	56.19		
Dyslipidemia	0.484	1.52	0.46	5.002	0.003	3.88	1.58	9.51	0.99	0.00	0.00	1.00		
Smoking	0.644	0.76	0.24	2.41	0.001	0.21	0.09	0.51	0.032	9.19	1.21	69.58		
Obesity	0.035	0.22	0.05	0.904	0.861	0.90	0.30	2.69	0.22	0.33	0.05	1.97		
Prothrombotic comorbidities	0.048	4.43	1.01	19.4	0.012	3.60	1.32	9.82	0.44	2.03	0.32	12.81		
IHD	0.262	2.26	0.54	9.42	0.095	1.91	0.89	4.11	0.99	3.69	0.00	1.00		
Anterior STEMI	0.046	4.37	1.02	18.59	<0.001	7.26	2.93	18.01	0.09	3.26	0.80	13.31		
IHD associated with CV risk factors	0.554	1.12	0.76	1.66	0.062	1.17	0.99	1.38	0.003	1.58	1.17	2.14		

IHD=previously documente ischemic heart disease, CV=cardiovascular, OR=Odds Ratio, 95% CI=OR confidence interval

over 40 years with the previously documented ischemic heart disease (Table 2). In all patients the no-reflow phenomenon correlated with the occurrence of necrosis and reduction below 30% of the ST-segment elevation on the ECG performed after primary PCI (Table 2).

By applying the multivariate logistic regression method the following were identified as independent predictors of the no-reflow phenomenon: anterior localization of STEMI and prothrombotic comorbidities in both men under 40 years and in those over 40 years, arterial hypertension in men under 40 years, dyslipidemia in patients over 40 years, diabetes mellitus, smoking and association of previously diagnosed IHD with cardiovascular risk factors in women over 40 years (Table 3).

## DISCUSSIONS

The relatively important frequency and negative prognosis of occurrence, persistence and refractoriness to treatment of the no-reflow phenomenon on the evolution post revascularization in acute myocardial infarction with ST segment elevation<sup>6,35,36</sup> has boosted the evaluation of potential risk factors in order to identify subgroups of patients with indication for prophylactic therapy, and there are studies showing that the reversibility of the no-reflow phenomenon reduces the risk of death after myocardial infarction<sup>6</sup>.

The frequency of the no-reflow phenomenon in patients with STEMI and primary interventional revascularization, assessed in this study by resting transthoracic Doppler echocardiography of coronary arteries was 27.5% and falls within the values reported in literature<sup>6,9,16,36</sup>. Reported frequency of the no-reflow phenomenon after acute myocardial infarction is of

2 – 50%, variations are due to the type of revascularization, diagnosis technique and time from onset of ischemic pain until coronary revascularization<sup>5,37,38</sup>, its frequency being reduced by shortening the time from onset of infarction until achieving coronary revascularization<sup>6,16,38</sup>. In our study that evaluated STEMI patients, who showed ST segment elevation without Q-wave on admission electrocardiogram, the mean time value recorded since the first pain of ischemic nature until primary PCI was 6 hours. The appearance in this study of the no-reflow phenomenon more common in women over 40 years (43.4%) is consistent with finding a higher frequency of this phenomenon in patients over 65 years with STEMI and revascularization by primary PCI<sup>39</sup>. As in other studies, women over 40 and STEMI presented themselves significantly later than men for determining the diagnosis of infarction<sup>40</sup>, aspect that may be involved in increasing the frequency of the no-reflow phenomenon in this subgroup of patients. In our study, the no-reflow phenomenon occurred significantly more often in men under 40 years (38.7%) than in those over 40 years (20%), one reason being the obstructive coronary lesion, predominantly thrombotic, described in men under 40 years, an aspect reported in literature that assessed the no-reflow phenomenon post STEMI in an invasive, angiographic manner<sup>6</sup>.

In this study, where the no-reflow phenomenon was assessed by transthoracic Doppler echography post PCI at the level of the coronary artery involved in STEMI, the data were consistent with those that used the coronary angiography and magnetic resonance imaging as a method of assessment, reporting a higher frequency of this phenomenon in patients with

anterior STEMI by LAD obstruction and thrombotic obstructive lesions<sup>6,41-43</sup>.

Chronic or acute systemic inflammatory diseases were positively correlated with the occurrence of the no-reflow phenomenon in men, regardless of age, aspect suggesting in this category of patients the involvement in the emergence of the no-reflow phenomenon of a possible concomitant lesion at microcirculation level and systemic inflammatory response associated with acute or chronic inflammatory diseases.

Arterial hypertension is in this study an independent predictor of the no-reflow phenomenon in young men, aspect discussed in literature in correlation with changes in secondary myocardial microcirculation due both to remodelling of the left ventricle with interstitial fibrosis and to the decrease of the coronary flow reserve by increasing vascular tone<sup>9,44</sup>. Dyslipidemia in men over 40 years and smoking in women over 40 years appear in this study as independent predictors of the no-reflow phenomenon, possibly because of the endothelial dysfunction that has been shown to be associated with these risk factors<sup>9</sup>. Some studies estimate that smoking is not a risk factor for the no-reflow phenomenon<sup>8</sup>, in our study smoking appears as independent predictor of the no-reflow phenomenon in women over 40 years. Diabetes mellitus occurs significantly more often in women over 40 years and is in this study an independent predictor for the occurrence of the no-reflow phenomenon in this subgroup, elevated blood sugar levels being also positively correlated with the no-reflow phenomenon in other publications<sup>45</sup>.

The previously documented ischemic heart disease, present in approximately 2/3 of women over 40 years, appears as a risk factor of the no-reflow phenomenon in combination with multiple cardiovascular risk factors. The observation of this study joins previous publications that showed that old myocardial infarction is associated with a high risk of the no-reflow phenomenon<sup>46,47</sup>.

We emphasize that our study assessed the no-reflow phenomenon in patients with STEMI and primary PCI without using protective devices of distal embolization, their use being followed in some clinical reports by reduction of the procedural myocardial infarction rate and no-reflow phenomenon rate<sup>48,49</sup>.

## CONCLUSIONS

The no-reflow phenomenon assessed by flow velocity parameters in the coronary artery involved in the infarction, obtained by transthoracic Doppler echocar-

diography, occurred in approximately 1/4 of STEMI patients revascularized by primary PCI and was also positively correlated, regardless of age and gender, with the anterior location of STEMI on ECG, LAD obstruction, coronary obstruction by a thrombus in young men and by atherosclerotic plaque in men over 40 years.

Intervention of arterial hypertension, diabetes mellitus, dyslipidemia, smoking and prothrombotic comorbidities in the occurrence of the no-reflow phenomenon appear to be modulated by age and gender.

## STUDY LIMITS

The subgroup of women under 40 years and STEMI was not a statistically significant sample to be included in the assessment.

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