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Myocardial remodeling in NSTEMI patients with intermediate and low cardiovascular risk exposed to delayed revascularization

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Abstract

Background: Nowadays, the impact of the delayed myocardial revascularization (DMR) (>72h) in patients with myocardium infarction without ST-segment elevation (NSTEMI) having either intermediate or low cardiovascular risk (ILCR) on quality of post-infarction myocardial remodeling is not well established. Aim of the study: The comparative evaluation of cardiac functional recovery of NSTEMI patients undergoing either revascularization <72h or DMR (72h–30 days) in a follow-up of 6 months.
Material and methods: The study was realized in 2 homogenic series of NSTEMI patients with ILCR exposed to revascularization: <72h (control) or to DMR (72h–30 days). The echocardiographic and physical test indices were registered at the 2nd day since revascularization and after 6 months.
Results: The increasing ratio of ejection fraction was significantly higher in patients with DMR compared to control (5.24% vs 1.73%). Likewise, the contractility ability of left ventricle improved better, proven by systolic volume diminution, lower value of akinetic areas, and less patients with class III of heart failure according to New York Heart Association (4 vs 29%). More than that, DMR was associated with higher physical endurance.
Conclusions: NSTEMI patients with ILCR exposed to delayed myocardial revascularization (72h–30 days) had a better post-infarction recovery after 6 months according to dynamics of echocardiographic and physical tolerance indices in comparison with patients revascularized <72h.
Key words: myocardial infarction, delayed revascularization, myocardial remodeling, echocardiographic indices.

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Introduction

The post-infarction remodeling of the myocardium is a complex phenomenon that activates the main systems of homeostasis, in the acute phase of myocardial necrosis and is marked by morpho-functional and metabolic changes meant to ensure the adaptation of the heart's contractility by reducing the number of sarcomeres. The quality of the post-infarction remodeling, defined by structural and geometrical changes in the first 4-6 months from the onset of the myocardial infarction (MI) will lately dictate the clinical and functional evolution of the patient as well as the major advanced cardiovascular events (MACE) rate. It obviously depends on a series of factors, but one of the most important is the necrosis area, that usually is widespread in the case of MI with elevated ST segment (STEMI) due to a total or subtotal occlusion (>90%) of a large caliber epicardial artery, associated with a conclusive inflammatory response.

MI without ST-segment elevation (NSTEMI), from the physiological point of view, remains an intriguing question and a challenge for most cardiologists due to the similar in-hospital mortality percent (5-7%) and even higher at one year distance, versus STEMI, despite its specificity of evolution in the limit of one coronary artery with a total occlusion just in ⅓ of cases but with a better distal collateralization than STEMI. In the rest, when the coronary occlusion is <50%, pathogenetically important, is attributed the role of microcirculatory coronary dysfunction, where the subendocardial coronary arteriola (<200 mkm) manifests a prothrombotic status, increased by the lasting spasm due to endothelial dysfunction.

In STEMI, the revascularization time of the "culprit" artery is a decisive factor for the prognosis of evolution post MI, the optimal accepted window is between 6 and 12 hours from the onset of the myocardial necrosis.

For NSTEMI, the European Society of Cardiology (ESC) guidelines recommendations regarding the timing of the invasive treatment are estimated through the 2 scores: Global Registry of Acute Coronary Events (GRACE) score and Thrombolysis In Myocardial Infarction (TIMI) score. In patients with high and very high cardiovascular risk, primary reperfusion is recommended at the distance of 2 and 24h respectively from the MI onset [1]. In patients with moderate or low cardiovascular risk (ILCR), the ESC guidelines recommend applying the invasive strategy in the first 72h from the establishment of NSTEMI diagnostic, and in case of the impossibility to perform the invasive treatment lo-

cally, the patient should be transferred to a medical center with interventional cardiology [2].

Our experience reveals the existence in the Republic of Moldova of a large number of patients eligible to this recommendation, mainly due to the newly installed social restrictions because of COVID-19 pandemic, that postpones the myocardial reperfusion even to 30 days.

It is important to emphasize, in this context, the impact of the delayed angioplasty on the prognosis of post MI evolution at distance in contiguity with the estimation of the character of the morpho-functional remodeling of the myocardium, functional class of heart failure according to New York Heart Association (NYHA) as well as on MACE rate.

Aim of the study: the comparative assessment of the effects of reperfusion <72 h and delayed reperfusion (72h–30 days), on echocardiographic parameters and physical endurance in NSTEMI patients at the 6 months distance.

Material and methods

The study was realized on two groups of NSTEMI patients with GRACE score <140 (intermediate and low cardiovascular risk), created depending on the angioplasty time:

- Group 1, control series (126 patients) revascularized <72 h;
- Group 2 (126 patients) revascularized in the time between 72h–30 days.

Both groups were considered homogeneous regarding the age, gender, the onset of comorbidities symptoms (hypertension, diabetes mellitus) and other cardiac risk factors (tab. 1).

Patients included in the study were investigated in the Institute of Cardiology and in the polyvalent hospital NOVAMED. The NSTEMI diagnostic was established on the base of the clinical, electrocardiographic, echocardiographic and enzymatic criteria: (i) the onset of symptoms of acute myocardial ischemia lasting more than 20 minutes, (ii) ST-segment depression more than 1.0 mm and/or T-wave changes in more than 2 leads on ECG and/or evidence of loss of viable myocardium or new regional wall motion abnormality and (iii) increase of cardiac biomarkers (CK-MB and cardiac Troponins TnT).

GRACE score was calculated via the standard formula, taking into consideration the age, heart rate (HR), systolic blood pressure (SBP), creatinine, ST-segment deviation on ECG, abnormal cardiac enzymes and history of cardiac arrest.

Exclusion criteria were:

- High and very high cardiovascular risk;
- History of myocardial infarction;
- Dilated cardiomyopathy;
- Post-inflammatory cardiomyopathy;
- Hypertrophic cardiomyopathy;
- Coronary stenosis that caused the infarct < 50% and FFR (Fractional Flow Reserve) > 0.80;
- The presence of stenosis > 75% on other vases than the one causing the MI;
- History of CABG (coronary artery bypass surgery) or PCI (Percutaneous Coronary Intervention);
- Significant valve disease (III-IV degree of insufficiency, moderate or severe stenosis);
- Diffuse LV (left ventricle) hypokinesis on ECHO (echocardiography);
- Severe renal failure.

The following examinations were done at admission and at a 6 months interval post MI:

Registration of ECG in 12 leads at rest, using the electrocardiographic device "CARDIOLINE AR1200adv" (Cardioline S.p.A, Italy) repeated three times: at admission, the day after revascularization and at a 6 months distance.

Transthoracic echocardiography (ECHO), realized using

Table 1. The clinical feature of NSTEMI patients on admission

Indices		General group (N = 252)	Group 1 (N = 126)	Group 2 (N = 126)	p
Age		59.940±0.639	59.675±0.919	60.206±0.891	>0.05
Gender:	Male	208 (82.5%)	104 (82.5%)	104 (82.5%)	>0.05
	Female	44 (17.5%)	22 (17.5%)	22 (17.5%)	
Resident:	Urban	149 (59.1%)	79 (62.7%)	70 (55.6%)	>0.05
	Rural	103 (40.9%)	47 (37.3%)	56 (44.4%)	
Occupation:	Sleep	10 (4.0%)	3 (2.4%)	7 (5.6%)	>0.05
	Physical effort	90 (35.7%)	44 (34.9%)	46 (36.5%)	
	Intellectual work	26 (10.3%)	14 (11.1%)	12 (9.5%)	
	Retired	126 (50.0%)	65 (51.6%)	61 (48.4%)	
Marital status:	Single	6 (2.4%)	5 (4.0%)	1 (0.8%)	>0.05
	Married	209 (82.9%)	103 (81.7%)	106 (84.1%)	
	Divorced	7 (2.8%)	3 (2.4%)	4 (3.2%)	
	Widower	30 (11.9%)	15 (11.9%)	15 (11.9%)	
Type of admission:	Emergency room	181 (71.8%)	124 (98.4%)	57 (45.2%)	<0.001
	Programmed	71 (28.2%)	2 (1.6%)	69 (54.8%)	
Main symptom:	Pain	234 (92.9%)	121 (96.0%)	113 (89.7%)	<0.05
	Dyspnea	17 (6.7%)	4 (3.2%)	13 (10.3%)	
	Palpitations	1 (0.4%)	1 (0.8%)	0 (0%)	

Presenting of symptoms:	At rest	107 (42.5%)	77 (61.1%)	30 (23.8%)
	Minor physical effort	101 (40.1%)	32 (25.4%)	69 (54.8%)
	Moderate physical effort	37 (14.7%)	12 (9.5%)	25 (19.8%)
	Major physical effort	7 (2.8%)	5 (4.0%)	2 (1.6%)
				<0.001
Onset of symptoms:	Sudden	168 (66.7%)	88 (69.8%)	80 (63.5%)
	Slow	84 (33.3%)	38 (30.2%)	46 (36.5%)
				>0.05
History of angina pectoris:	Yes	79 (31.3%)	35 (27.8%)	44 (34.9%)
	No	173 (68.7%)	91 (72.2%)	82 (65.1%)
				>0.05
Angina's functional class in history:	I	0 (0%)	0 (0%)	0 (0%)
	II	14 (17.7%)	6 (17.1%)	8 (18.2%)
	III	51 (64.6%)	24 (68.6%)	27 (61.4%)
	IV	0 (0%)	0 (0%)	0 (0%)
	Unstable angina	14 (17.7%)	5 (14.3%)	9 (20.5%)
				>0.05
Nitrate administration:	No	230 (91.3%)	114 (90.5%)	116 (92.1%)
	Yes	22 (8.7%)	12 (9.5%)	10 (7.9%)
				>0.05
Risk factors				
Hypertension HTA:	absent	76 (30.2%)	49 (38.9%)	27 (21.4%)
	Gr. I	3 (1.2%)	2 (1.6%)	1 (0.8%)
	Gr. II	87 (34.5%)	37 (29.4%)	50 (39.7%)
	Gr. III	86 (34.1%)	38 (30.2%)	48 (38.1%)
				<0.05
Obese or overweight:	No	106 (42.1%)	46 (36.5%)	60 (47.6%)
	Yes	146 (57.9%)	80 (63.5%)	66 (52.4%)
				>0.05
Diabetes Mellitus:	No	193 (76.6%)	99 (78.6%)	94 (74.6%)
	Yes	59 (23.4%)	27 (21.4%)	32 (25.4%)
				>0.05
Dyslipidemia:	No	136 (54.0%)	73 (57.9%)	63 (50.0%)
	Yes	116 (46.0%)	53 (42.1%)	63 (50.0%)
				>0.05
Family history:	Present	44 (17.5%)	26 (20.6%)	18 (14.3%)
	Absent	208 (82.5%)	100 (79.4%)	108 (85.7%)
				>0.05
Physical activity:	<30 min/day	143 (56.7%)	75 (59.5%)	68 (54.0%)
	>30 min/day	109 (43.3%)	51 (40.5%)	58 (46.0%)
				>0.05
Smoking:	No	175 (69.4%)	84 (66.7%)	91 (72.2%)
	Yes	77 (30.6%)	42 (33.3%)	35 (27.8%)
				>0.05
Alcohol intake:	No	214 (84.9%)	100 (79.4%)	114 (90.5%)
	Regular	32 (12.7%)	20 (15.9%)	12 (9.5%)
	Exaggerated	6 (2.4%)	6 (4.8%)	0 (0%)
				<0.05
Coffee consumption:	No	206 (81.7%)	100 (79.4%)	106 (84.1%)
	Yes	46 (18.3%)	26 (20.6%)	20 (15.9%)
				>0.05
Physical examination				
Hight		170.806±0.281	170.810±0.412	170.802±0.385	>0.05
Weight		77.579±0.618	78.786±0.895	76.373±0.843	>0.05
Body weight index		26.537±0.173	26.940±0.261	26.133±0.222	<0.05
Systolic blood pressure		134.786±1.310	134.460±1.909	135.111±1.803	>0.05
Diastolic blood pressure		81.710±0.751	80.952±1.069	82.468±1.056	>0.05
Heart rate		75.087±0.809	76.984±1.109	73.190±1.158	<0.05

the device "PHILIPS Hd11 Xe" (Koninklijke Philips N.V., Holland) in M, B and Doppler mode with a 2.0-2.5 mHz transducer. The functional and geometrical parameters regarding structural and functional remodeling were estimated.

The stress test was performed using the cycloergometric device (CEM) "CARDIOLINE cube stress" (Cardioline S.p.A, Italy) through the continuous method, pedaling speed was 60 rotations per minute, starting from 25 Wt, and every step was taking 2 minutes. ECG, HR and SBP were constantly monitored. At each step the load was increased by 25 Wt.

The criteria for stopping the test were:

- Reaching the target criteria, 85% from the maximal HR (220 – age in years);
- A strong angina seizure;
- Severe dyspnea;
- Ischemic changes on ECG;
- Set of rhythm abnormalities (frequent extrasystole, atrial fibrillation, etc.);
- Lowering BP less the initial one or elevation more than 230/130 mm Hg;
- Claudication – ischemic pain in the inferior extremities;

The test was considered positive in the case when the elevation or depression of ST segment > 1 mm at 0.08 sec from the j point was registered, compared with the ECG at rest.

The coronarography was conducted in the catheterization laboratories in the Institute of Cardiology and in the

Table 2. Main echocardiographic parameters from NSTEMI patients on the 2nd day after revascula

Parameters	Group 1	Group 2	p
LV diastolic diameter (mm)	53.556±0.475	52.437±0.507	>0.05
LV diastolic volume (ml)	148.341±2.653	144.016±2.240	>0.05
LV systolic diameter (mm)	36.762±0.579	35.683±0.550	>0.05
LV systolic volume (ml)	75.294±2.055	70.627±1.773	>0.05
Interventricular septal wall (mm)	11.500±0.154	11.849±0.150	>0.05
LV posterior wall (mm)	10.274±0.090	10.389±0.128	>0.05
Ejection fraction (EF) (%)	47.063±0.785	48.754±0.748	>0.05
Normokinetic pattern No	112 (88.9%)	108 (85.7%)	>0.05
Normokinetic pattern Yes	14 (11.1%)	18 (14.3%)	>0.05
Relaxation disorders Yes	118 (93.7%)	120 (95.2%)	>0.05
Relaxation disorders No	118 (93.7%)	120 (95.2%)	>0.05

polyvalent hospital NOVAMED, using the device General Electric INNOVA and Siemens "Artis One".

Depending on the degree of stenosis, the coronary lesions were divided in (1) insignificant lesions (25%); moderate (25-50%); moderate-severe (51-75%); severe (76-90%); critical (91-99%) and total occlusion (100%). In the case of severe, critical and total occlusion lesions feasibility of collateralization was estimated.

After revascularization and stenting the "culprit" artery, on the final flow was applied the TIMI system score and myocardial "blush" (MBG – Myocardial Blush Grade).

Optical Coherence Tomography (OCT) was realized with the "Saint Jude Medical" device, model "ILUMIEN" just in the case of those patients whose morphologic pattern couldn't be appreciated through coronary angiography.

Fractional flow reserve (FFR*)* was estimated with the "Saint Jude Medical" device, model "ILUMIEN" in those patients who were suspected to have abnormality in coronary microcirculation, as a result of a moderate coronary stenosis diagnosed during coronary angiography.

Laboratory investigations have included a large specter of circulating markers regarding: irreversible cellular lesions, dyslipidemia, endothelial dysfunction, systemic inflammation, hyperglycemia, hemostasis, etc.

The angioplasty was realized, using 2 types of stents: bare metal stent (BMS) and drug eluting stent (DES). The diameter of the used stents was in the range from 2.25 mm to 5 mm, while the length between 8 mm and 48 mm.

For the statistical processing of the numerical material, were used the accepted biostatistical maneuvers: t-Student index (comparison of averages in 2 groups), ANOVA (comparison of averages in 3 groups), method of variational analysis, correlation, $\chi 2$ index (comparison of nonparametric variables), Pearson correlation coefficient, U-Fischer criterion. Statistically significant in all methods of analysis was considered the value $p < 0.05$.

Results

The echocardiographic data from NSTEMI patients estimated on the 2nd day after angioplasty are similar in both groups (without significant discrepancy) and prove the imminent morphofunctional pattern of failed heart (tab. 2).

The ejection fraction was average in both groups, below 49%, that associated with elevated left ventricular end diastolic volume (LVEDV) that exceeded on average 144 ml. Interventricular septal wall (IVSW) and left ventricular posterior wall (LVPW) thickness, that are considered an important index in appreciation of myocardial hypertrophy degree, registered values above 11 mm and 10 mm respectively for both groups.

Except for the rate of severe stenosis and total occlusions in the second group *versus* the first group, data obtained during coronarography are similar (tab. 3).

Table 3. Coronarography data of the NSTEMI patients

Index		Group 1	Group 2	p
Approach:	Radial	108 (85.7%)	119 (94.4%)	
	Femoral	13 (10.3%)	6 (4.8%)	>0.05
	Brachial	5 (4.0%)	1 (0.8%)	
Atherosclerotic lesions:				
	1 coronary	32 (25.4%)	30 (23.8%)	>0.05
	2 coronaries	22 (17.5%)	23 (18.3%)	
	3 coronaries	72 (57.1%)	73 (57.9%)	
"Culprit" artery:	LM	1 (0.8%)	0 (0%)	>0.05
	LAD I	43 (34.1%)	25 (19.8%)	
	LAD II	30 (23.8%)	39 (31.0%)	
	LAD III	2 (1.6%)	2 (1.6%)	
	DIA	1 (0.8%)	3 (2.4%)	
	aCX I	4 (3.2%)	0 (0%)	
	aCX II	8 (6.3%)	15 (11.9%)	
	aCX III	3 (2.4%)	0 (0%)	
	OM	1 (0.8%)	3 (2.4%)	
	RCA I	10 (7.9%)	10 (7.9%)	
	RCA II	15 (11.9%)	16 (12.7%)	
	RCA III	8 (6.3%)	13 (10.3%)	
Lesion degree of the target segment:	25-50%	1 (0.8%)	1 (0.8%)	<0.01
	50-75%	3 (2.4%)	1 (0.8%)	
	75-90%	7 (5.6%)	16 (12.7%)	
	90-99%	38 (30.2%)	58 (46.0%)	
	Total occlusion	77 (61.1%)	50 (39.7%)	
Distal recharge:	No	43 (39.8%)	28 (28.3%)	>0.05
	Yes	65 (60.2%)	71 (71.7%)	
Recharge type:				
Intrasystemic collateral		19 (25.0%)	21 (24.7%)	>0.05
Extrasystemic collateral		22 (28.9%)	14 (16.5%)	
Intra-extrasystemic collateral		9 (11.8%)	11 (12.9%)	
Anterograde *via* thrombus		37 (48.7%)	43 (50.6%)	

Angiographic aspect of: Atherosclerotic plaque		60 (47.6%)	87 (69.0%)	<0.01
Thrombotic masses		66 (52.4%)	39 (31.0%)	
Lesion length:	0-15 mm	33 (26.2%)	39 (31.0%)	>0.05
	16-25 mm	71 (56.3%)	70 (55.6%)	
	26-40 mm	17 (13.5%)	15 (11.9%)	
	>40 mm	5 (4.0%)	2 (1.6%)	
Calcification:	0	72 (57.1%)	65 (51.6%)	>0.05
	1	36 (28.6%)	51 (40.5%)	
	2	12 (9.5%)	5 (4.0%)	
	3	6 (4.8%)	5 (4.0%)	
Tortuosity:	0	48 (38.1%)	43 (34.1%)	>0.05
	1	58 (46.0%)	55 (43.7%)	
	2	19 (15.1%)	28 (22.2%)	
	3	1 (0.8%)	0 (0%)	
Bifurcation:	No	105 (83.3%)	98 (77.8%)	>0.05
	Yes	21 (16.7%)	28 (22.2%)	

One of the notable points for estimating the quality of post-myocardial infarction remodeling is the severity of heart failure. It is remarkable that a higher rate of patients with NYHA II in group 2 compared to group 1 at a 6 months interval after angioplasty (66.7 vs 52.4%) while the rate of NYHA III, on the contrary is significantly lower (4 vs 29%).

This observation indicates a better functional heart recovery in NSTEMI patients treated with postponed revascularization, at 72 h. In this aspect, the dynamics of echocardiographic indices attested at a distance of 6 months after revascularization is also intelligible (tab. 4).

It is important to mention a more significant increase of EF in group 2 *versus* group 1 (5.24% vs 1.73%) that is also associated with a notable LV contractility recovery visible through a 5.56% decrease of LV end systolic volume meanwhile it increased by 1.05% in the control group. A similar dynamic was observed regarding LV systolic diameter.

Table 4. Relative deviations (%) of echocardiographic parameters among a period of 6 months

Parameters	Group 1			Group 2			P
	M	m	p	M	m	p	
Left atrium diameter	+0.484	0.191	<0.05	-0.341	0.136	<0.05	<0.01
LV diastolic diameter	+1.097	0.210	<0.001	+1.103	0.434	<0.05	>0.05
LVEDV	+2.742	1.028	<0.01	+0.944	1.128	>0.05	>0.05
LV systolic diameter	+0.508	0.302	>0.05	-1.960	0.243	<0.001	<0.001
LV end systolic volume	+1.048	1.080	>0.05	-5.556	0.615	<0.001	<0.001
IVSW	-0.121	0.09	>0.05	-0.159	0.05	<0.01	>0.05
LVPW	-0.085	0.06	>0.05	+0.071	0.05	>0.05	>0.05
EF	+1.734	0.58	<0.01	+5.238	0.36	<0.001	<0.001
Right ventricle diameter	-0.177	0.18	>0.05	-0.683	0.23	<0.01	>0.05
Right atrium	+0.637	0.24	<0.01	-0.175	0.19	>0.05	<0.01
Pulmonary systolic arterial pressure	-7.113	0.65	<0.001	-9.873	0.48	<0.001	<0.01
hypokinetic areas	+1.135	0.12	<0.001	+1.397	0.12	<0.001	>0.05
akinetic areas	-0.095	0.1	>0.05	-0.159	0.07	<0.05	<0.05
dyskinetic areas	-0.325	0.09	<0.001	-0.04	0.04	>0.05	<0.01
areas involved in the aneurysm	-0.294	0.08	<0.001	-0.048	0.05	>0.05	<0.01

Table 5. The results of the stress test at NSTEMI patients 6 months after revascularization

Parameter		General group	Group 1	Group 2	p
Initial systolic blood pressure (SBP)		124.627±0.735	124.202±1.120	125.032±0.962	>0.05
Initial diastolic blood pressure (DBP)		70.656±0.591	71.639±0.889	69.720±0.777	>0.05
Initial heart rate (HR), 1/min		67.545±0.402	68.151±0.613	66.968±0.520	>0.05
Max intensity effort, Wt		105.430±1.710	99.370±2.487	111.200±2.244	<0.001
Total time of physical effort, min		8.898±0.159	8.319±0.234	9.448±0.205	<0.001
Max SBP at effort, mm Hg		187.705±1.120	186.261±1.708	189.080±1.457	>0.05
Max DBP at effort, mm Hg		101.631±0.771	100.504±1.073	102.704±1.100	>0.05
Max HR, 1/min		134.377±1.379	131.773±2.187	136.856±1.686	>0.05
Reached target HR, 1/min	No	50 (20.5%)	37 (31.1%)	13 (10.4%)	<0.001
	Yes	194 (79.5%)	82 (68.9%)	112 (89.6%)	
Stress test conclusion:	Positive	8 (3.3%)	7 (5.9%)	1 (0.8%)	<0.001
	Negative	192 (78.7%)	80 (67.2%)	112 (89.6%)	
	Inconclusive	43 (17.6%)	31 (26.1%)	12 (9.6%)	
	Dubious	1 (0.4%)	1 (0.8%)	0 (0%)	
Effort tolerance:	Low	30 (12.3%)	23 (19.3%)	7 (5.6%)	<0.01
	Medium	119 (48.8%)	58 (48.7%)	61 (48.8%)	
	High	95 (38.9%)	38 (31.9%)	57 (45.6%)	
	Very high	0 (0%)	0 (0%)	0 (0%)	
	Very low	0 (0%)	0 (0%)	0 (0%)	

From a pathophysiologic point of view, the decrease of right ventricle (RV) dimension in association with reduction of pulmonary pressure index in both groups is important.

Regarding the dynamics of the kinetic changes of the heart in the post-infarction remodeling, the phenomenon of diminution of dyskinetic areas, akinetic areas and risk areas for aneurysm in both groups are important, that subsequently influences the EF. On the other hand, the sum of hypokinetic areas increased to an incremental value similar in both groups.

The positive heart changes developed during the post-infarctional period are followed by an improved tolerance to physical effort (tab. 5).

It is worth noting that the intensity of the maximum effort made by patients in group 2 was considerably higher compared to group 1: 111.200±2.244 vs 99.370±2.487 Wt ($p<0.001$). The total effort time also became significantly longer, with an average delay of 1.1 min: 9.448±0.205 vs 8.319±0.234 min ($p<0.001$). Was documented as well, a larger number of patients that reached the aimed HR: 89.6% vs 68.9%.

The cumulative benefit of physical endurance in patients at the end of 6-month period after revascularization of NSTEMI, was manifested with high physical tolerance at a much higher rate in the case of delayed angioplasty compared to angioplasty in the first 72 hours: 45.6% vs 31.9%.

Summarizing, delayed revascularization in NSTEMI patients with intermediate and low cardiovascular risk, applied at a 72 h- 30 day distance, proved at 6 months a morphofunctional heart remodeling comparable to the pattern of imminent revascularization applied in the first 72 hours, more than that, some changes are even more conclusive: (1) increase of EF, (2) decrease of LVSV and LVSD, (3) the rate of NYHA II patients, (4) maximal exercise intensity, total physical effort time, and rate of patients with high tolerance to physical effort.

Discussion

The crucial difference in addressing invasive treatment of NSTEMI patients with intermediate and low cardiovascular risk calculated by GRACE score (<140) was determined by the revascularization time: <72h and between 72h and 30 days (delayed revascularization). Results obtained at a distance of 6 months, on the restoration of ECHO indices and tolerance to physical effort, as a reflection of the heart's ability of a post-infarction remodeling, proved to be better in the case of postponed revascularization. This phenomenon reveals new perspectives in the application of angioplasty in this type of patients and may basically serve as an indispensable maneuver of time variable.

Several plausible hypotheses of exegesis and explanation of these benefits exist.

First of all, patients with NSTEMI had an intermediate and low cardiovascular risk according to GRACE score and the coronary stenoses >75% didn't exist. Likewise, the collateral system in the ischemic myocardium zone was quite well developed (the phenomenon of distal coronary artery recharge on coronary angiography was present in 65.7% of patients). Revascularization applied during the first 72 hours coincides with the peak of the inflammatory response, cytokine expression, blood cell infiltration, and due to this, the maximum activity of oxidative stress. Thus, the expected benefit of revascularization is compromised by the detrimental action of these factors. It is well known that the maximum expression of neutrophils in the area of myocardial necrosis occurs within 24-48 hours, while the expression of proinflammatory macrophages (M_1) is found at maximum proportion in the period 48-72 hours [3].

Second of all, delayed revascularization occurs during the period of natural restoration of the intrinsic antioxidant potential, after the ischemic impact, and the power of the oxygen paradox inherent to revascularization is thus depreciated, especially after 72 hours when the expression of anti-inflammatory macrophages (M_2) increases [4, 5].

Third of all, the traumatic impact of delayed revascularization occurs due to a longer and more consistent metabolic remodeling, its main elements being the expression of the growth transformation factor (TGF-β) induced by anti-inflammatory cytokines, which increases the intracellular expression of "heat-shock" proteins, recognized as factors in ensuring the resistance of cells to the action of various endogenous and exogenous lesions [6, 7].

Another important thing, in the patients of group 2 the ratio of atherosclerotic/thrombotic lesions of the "culprit" artery was higher than 1. In the group with revascularization <72 hours, on the contrary, this ratio was <1. Therefore, the prevalence of atherosclerotic paternal coronary lesion is a precondition for a better post-procedural evolution of the myocardial remodeling process compared to the predilection of thrombotic paternal. The latter has an increased risk of post-procedural thromboembolism and the phenomenon of 'low-reflow' or 'non-reflow' during reperfusion, inclusive in patients with MI and elevated ST segment [8, 9]. Deep embolization affects the subendocardial microcirculation and may in the context of «low-reflow» and «non-reflow» phenomena trigger the development of the sidereal and hibernated myocardium. This factor may possibly have conditioned higher LVESV values in patients with NSTEMI treated by revascularization <72 hours at a distance of 6 months.

Altogether, these arrangements may have the significance of beneficial preconditions for the cumulative impact of delayed myocardial revascularization in NSTEMI patients on post-infarction morphofunctional remodeling and clinical evolution.

Another element that should be noticed is that among the factors that determined the benefit of delayed revascularization is the presence of a lower rate of patients with total occlusion of the coronary artery in group of NSTEMI patients exposed to DMR: 39.7% vs. 48.7%. In the VERDICT trial, the rate of NSTEMI patients, in which the coronary angiography examination identified total occlusion, reached 26.6% [10].

Among the caliber trials in which delayed revascularization was applied, the ISAR-COOL study should be mentioned, which excelled in an average angioplasty time of 86 hours and showed benefits similar to our research.

In the ICTUS study, the analysis of the death rate of NSTEMI patients at a distance of 10 years, did not prove conclusive benefits for revascularization <72 hours [11].

Finally, the analysis of the obtained results appeals to some conceptually and practically significant hypotheses:

• Delayed revascularization of patients with intermediate and low risk NSTEMI caused by total coronary occlusion would have a similar benefit to revascularization <72 hours, regarding post-infarction morphofunctional remodeling of the myocardium.

• In case of delayed revascularization of NSTEMI patients with intermediate and low cardiovascular risk, caused by stenosis <50%, the superiority of efficacy over revascularization <72 hours is plausible. In this context, the prompt and accurate diagnosis by use of instrumental markers (e.g. Magnetic resonance imaging) is important. Likewise, it is opportune the use of veritable circulatory markers of coronary microcirculation disorder responsible for subendocardial infarction, especially when cardiac troponins (TnT and TnI) dynamics and ECG outcomes are uncertain. Our experience based on applying of multi-marker strategy validates the predictive value of the markers which refer to the inflammatory response, oxidative stress, endothelial dysfunction and prothrombotic status.

Conclusions

1. In our study, delayed myocardial revascularization (72 hours - 30 days) applied for treatment of NSTEMI patients with intermediate and low cardiovascular risk, had proved the superior benefits in concern to clinical-functional evolution at a 6 months follow-up period compared to revascularization <72 hours.

2. The most important traits of delayed myocardial revascularization benefit are: (i) greater increase of EF, (ii) decrease in both LV end systolic volume and LV systolic diameter, (iii) increase in the number of patients with NYHA II and the reduction of NYHA III cases, as well as physical endurance boosting, manifested by double more patients, who fulfilled maximal physical endeavor.

References

1. Bennet G, Naoki M, Khaled MZ. Revascularization strategies for Non-ST-Elevation myocardial infarction. Curr Cardiol Rep. 2019;21(5):39. doi: 10.1007/s11886-019-1125-9.
2. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3):267-315. doi: 10.1093/eurheartj/ehv320.
3. Westman PC, Lipinski MJ, Luger D, et al. Inflammation as a driver of adverse left ventricular remodeling after acute myocardial infarction. J Am Coll Cardiol. 2016;67(17):2050-2060. doi: 10.1016/j.jacc.2016.01.073.
4. Viola A, Munari F, Sánchez-Rodríguez R, Scolaro T, Castegna A. The metabolic signature of macrophage responses. Front Immunol. 2019;10:1462. doi: 10.3389/fimmu.2019.01462.
5. Ley K. M1 means kill; M2 means heal. J Immunol. 2017;199(7):2191-2193. doi: 10.4049/jimmunol.1701135.
6. Hanna A, Frangogians NG. The role of TGF-β superfamily in myocardial infarction. Front Cardiovasc Med. 2019;6:140-149. doi: 10.3389/fcvm.2019.00140.
7. Yousefi F, Shabaninejad Z, Vakili S, et al. TGF-β and WNT signaling pathways in cardiac fibrosis: non-coding RNAs come into focus. Cell Commun Signal. 2020;18(1):87. doi: 10.1186/s12964-020-00555-4.
8. Yang L, Cong H, Lu Y, et al. Prediction of no-reflow phenomenon in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Medicine. 2020;99(26):e20152. doi: 10.1097/MD.0000000000020152.
9. Januszek R, Siudak Z, Malinowski K, et al. Aspiration thrombectomy in patients with acute myocardial infarction – 5-year analysis based on a large national registry (ORPKI). J Clin Med. 2020;9(11):3610. doi: 10.3390/jcm9113610.
10. Kofoed K, Kelbaek H, Hansen P, et al. Early versus standard care invasive examination and treatment of patients with Non-ST-Segment elevation acute coronary syndrome. Circulation. 2018;138(24):2741-2750. doi: 10.1161/CIRCULATIONAHA.118.037152.
11. Hoedemaker NPG, Damman P, Woudstra P, Hirsch A, Windhausen F, Tijssen JGP, et al. Early invasive versus selective strategy for non-ST-segment elevation acute coronary syndrome: the ICTUS trial. J Am Coll Cardiol. 2017;69(15):1883-1893. doi: 10.1016/j.jacc.2017.02.023.

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AS described the material and methods; LC presented introduction. IM wrote the abstract; IP exposed results; VC depicted discussion and corrected the text of the manuscript; MP initiated the idea of this research and revised the manuscript. All the authors revised and approved the final version of the manuscript.

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Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of the Institute of Cardiology, protocol No 04 of March 03, 2020. The informed consent was received from every patient.

Conflict of Interests

No competing interests were disclosed.