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THE INFLAMMATORY RESPONSE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION WITH ST SEGMENT ELEVATION DURING THE DEVELOPMENT OF ADAPTIVE AND PATHOLOGICAL REMODELING OF THE MYOCARDIUM

321.03 - CARDIOLOGY

Summary of the doctoral thesis in Medical Science

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CONCEPTUAL GUIDELINES OF RESEARCH

Actuality. ST-elevation acute myocardial infarction (STEMI) is the most severe form of myocardial infarction associated with increased morbidity and mortality.

Primary mechanical revascularization of the myocardium by coronary angioplasty in patients with STEMI performed in the first 12 hours after the onset of infarction has become the therapeutic option of choice, leading according to data from various meta-analyzes, to the decrease of in hospital mortality and in time distance mortality, as well [1,2]. However, STEMI remains a current and intricate problem of cardiology, dictated by the unstable clinical evolution in the post-infarction period caused by exacerbation of heart failure and the high incidence of major cardiovascular events (MACE), such as repeated acute myocardial infarction (MI), unstable angina, arrhythmias or stroke. The results of several studies demonstrate the evolution of MACE over a post-infarction period of 1-10 years at rates of 4.2-51% [3,4].

One of the determining factors of post-infarction MACE risk in patients with STEMI is the quality of post-infarction myocardial remodeling. The remodeling involves a set of structural and geometric changes of the heart, which are triggered by cardiomyocyte necrosis and end on average after 4-6 months from the time of revascularization [5,6]. LV dilatation at the end of post-infarction remodeling of the myocardium is the echocardiographic predictor of the pathological pattern of remodeling and is manifested by an increase of > 20% in indices, which characterizes the phenomenon of dilation, compared to admission parameters: end-diastolic volume and end-diastolic pressure of LV [7,8]. Assessment of the factors that contribute the development of PMR or AMR is important for the reinforcement of the algorithm for the post-infarction prognosis predictors in patients with STEMI favorable in the optimization of long-term therapeutic management [9].

The hypothesis of the study is based on the evidence of the presence of the inflammatory response triggered by myocardial necrosis in the first hours after the onset of ischemic injury. Inflammation defines the extension of the necrotic area. On the other hand, inflammation triggers and governs the process of removing dead cells by phagocytosis, as well as the repair of damaged myocardium by stimulating collagen synthesis through the action of cytokines (primarily interleukins and growth factors) and activation of cardiomyocyte hypertrophy genes [10, 11].

Although the role of inflammation is certified in the genesis of coronary heart disease and heart failure, as well as in the pathogenesis of ischemia-reperfusion impact [12], studies evaluating the link between the inflammatory response and the pattern of post-myocardial remodeling in patients with STEMI with the purpose of assessing the ratio between the dynamic of pro- and anti-inflammatory markers especially in the acute phase of infarction were not realized. At the same time, the correlation between the type of change of inflammatory markers in the acute phase and the markers of fibrillar collagen type III and type I turnover at the distance of 1- and 3-months post-infarction were not determined.

Although the pathogenesis of post-infarction HF is studied over several decades, some conceptual issues such as: the mechanism of compensation and decompensation of the heart in hemodynamic effort, the impact of ischemia-reperfusion, the peculiarities of myocardial inotropism to the action of neuroendocrine factors and the coronary phenomenon, the plausibility of the functional benefit in attenuating the inflammatory response and / or potentiating the action of anti-inflammatory markers, remain unclear.

Some answers can be found through experimental research, using in vitro isolated heart perfusion models, which allow the reproduction of different types of effort with volume, resistance, or ischemic impact. More other, particularities of the functional benefit of the inflammatory response modulation, based on the principles of anti-cytokine treatment, could be studied.

Aim: to evaluate the serum level of inflammation markers during the development of post-myocardial remodeling in patients with STEMI, as well as the particularities of the reactive effort of the heart and coronary system in experimental myocardial infarction, to predict the type of myocardial remodeling.

Research objectives:

1. Evaluation of the dynamic of serum levels of pro- and anti-inflammatory markers in the acute phase of infarction in patients with STEMI who develop adaptive or pathological post-infarction remodeling.

2. Evaluation of serum levels of pro- and anti-inflammatory markers at a distance of 1 and 3 months after revascularization in patients with STEMI who develop adaptive or pathological post-infarction remodeling.

3. Evaluation of serum levels of type III and type I fibrillar collagen turnover markers at a distance of 1 and 3 months, respectively, from revascularization of patients with STEMI in contiguity with the particularities of quantitative changes of pro- and anti-inflammatory markers in the acute phase of heart attack.

4. Evaluation of the mechanisms of danger of cardiac and coronary reactivity in experimental myocardial infarction, as well as of the effect of the anti-inflammatory treatment performed by the TNF-α and IL-10 antagonist.

5. Strengthening of the algorithm of biochemical markers with predictive value on the pattern of development of post-infarction remodeling in patients with STEMI, as well as functional predictors on the exacerbation of post-infarction heart failure.

Scientific novelty and originality. For the first time, a complex clinical-experimental study designed on acute myocardial infarction was performed to highlight the biochemical predictors of the pattern of post-myocardial remodeling of the myocardium (adaptive vs. pathological) in patients with STEMI undergoing angioplasty, as well as for in vitro evaluation of reactive features hemodynamic and neuroendocrine exertion of the heart and coronary system in experimental myocardial infarction (EMI). The daily dynamic for 1 week (acute infarction phase) of the pro- and anti-inflammatory markers were determined in patients with adaptive or pathological post-infarction remodeling to strengthen the marker algorithm with predictive value in this sense. For the first time, serum levels of markers of synthesis and degradation of type III (PIIICP and CIIITP) and type I fibrillar collagen (PICP and CITP) were estimated at a distance of 1 and 3 months after revascularization in correlation with the changes of acute anti-inflammatory markers. For the first time *in vitro*, the Vanhoutte phenomenon was assessed related to coronary reactivity in the model of EMI reproduced in rats, as well as the effect of attenuating inflammation by repeated administration of TNF-α and IL-10 antagonist.

Theoretical significance. The conceptual aspect regarding the role of the inflammatory response in the acute phase of the infarction reguarding the evolution of the pattern of post-myocardial remodeling of the myocardium in STEMI patients undergoing angioplasty is completed. The pathophysiological contribution of the anti-inflammatory markers, IL-4 and IL-10 in the acute phase of infarction is proven, they indicate the character of the post-infarct remodeling:

adaptive remodeling, when the circulating level of these markers rises by more than 50% from the 3rd day (expression of macrophages M1) to the 7th day (expression of macrophages M2) or pathological remodeling if the increase in their circulating level <5.5%. Certain evidences regarding the role of excessive activation of extracellular matrix (MEC) metalloproteinases are shown, in the pathogenesis of pathological myocardial post-infarction remodeling, and elevation of more than 50% of normal CIIITP and CITP at 1 and 3 months after revascularization of STEMI patients has a predictive meaning of PMR risk. The dynamic of anti-inflammatory markers (IL-4 and IL-10) that elevates <5.5% between the 3rd and 7th day post-infarction is connected to the increase by over 50% of interstitial fibrillar collagen degradation markers. At the same time, the mechanisms underlying the worsening of the evolution of post-infarct heart failure in the stress tests reproduced on the isolated heart, which are imposed by the incompetence of the isovolumic phase of relaxation and contraction, and negative myocardial inotropism to endothelin (ET-1) are not disturbed, as well as the involvement of the Gregg coronary phenomenon dependent on the vascular endothelium or the coronary response mediated by the mechanism of repolarization of the muscular environment.

Applied value. Strengthening the algorithm for predicting the risk of pathological myocardial remodeling in patients with STEMI by determining the dynamic of anti-inflammatory markers, IL-4 and IL-10, in the acute phase of the infarction, as well as the serum content of the degradation marker type I and III collagen at a distance of 1-3 months after revascularization. Highlighting the functional predictors of the exacerbation of the evolution of post-infarction heart failure, through echocardiographic indices that characterize the isovolumic phase of relaxation and contraction of the myocardium. Elevation of the circulating level of ET-1 is announced to be a danger factor for the adaptation of the heart to resistance exercise, given the negative inotropic effect of the myocardium on the action of the oligopeptide. The reduction of inflammation by TNF-α and IL-10 antagonist improves the functionality of the heart and the ability of its adaptation to hemodynamic and neuroendocrine changes and may thus be an important element of the therapeutic strategy applied in the acute phase of STEMI patients to prevent PMR development, when the elevation of circulating levels of IL-4 and IL-10 between day 3 and day 7 has an increase <5.5%.

Implementation. The results of the study were implemented in the clinical activity of the Institute of Cardiology, Polyvalent Hospital ”Novamed” and in the teaching process at the State University of Medicine and Pharmacology "Nicolae Testemițanu".

Scientific results approval. The research results were presented and discussed at the following national and international scientific forums: State Program 2020-2023 "Evaluation of instrumental and biochemical markers in the management of patients with acute myocardial infarction without ST-segment elevation, as well as in assessing the degree of microvascular coronary impairment" ; Congresses of the European Society of Cardiology (2017, 2018, 2019, 2020); VII th Congress of the Society of Cardiologists of the Republic of Moldova, October 9-10, 2020; "European Congress of Cardiology" and "World Congress of Cardiology", Paris, France August 31 - September 4, 2019; Theoretical course “Acute coronary syndrome through the prism of the guide for myocardial revascularization ”, USMF“ Nicolae Testemitanu ”, February 2019; National Congresses of the Romanian Society of Cardiology (Sinaia 2017, 2018, 2019); Annual Scientific Conference of the Medical University, at the State University of Medicine and a “Nicolae Testemitanu” Pharmacy, Chisinau, October 15-18, 2019; Conference “Cardio Forum

2018, Multidisciplinary Approach in Medical Practice", Chisinau October 12-13, 2018; Bucovinian International Medical Congress, Chernivtsi, April 5-7, 2017.

The thesis was discussed, approved and recommended for defense at the meeting of the Laboratory of Interventional Cardiology (protocol no.3 of 28/01/2019), at the Scientific 321.03 Cardiology Seminar (protocol no.3 of 01/07/2019) , Scientific Council of the Consortium (protocol no. 5 / 4.7 of 03/07/2020), IP "Nicolae Testemițanu" State University of Medicine and Pharmacy, Republic of Moldova.

Publications. The scientific results were reflected in 33 scientific papers (11 national, 21 international, 1 single author), 3 of which, in the international databases ISI and SCOPUS, 2 articles in journals from the National Register of profile journals, category B +; 10 articles in unreviewed national journals, 18 abstracts in national and international conferences.

Keywords. STEMI infarction, anti-inflammatory markers, myocardial infarction by isoproterenol, biochemical markers, functional indices, anticytokinic treatment.

Volume and structure. The thesis is presented on 110 pages, includes annotation (in Romanian, Russian, English), list of abbreviations, list of figures and tables, introduction, 4 chapters, results, general conclusions and practical recommendations, bibliography of 115 titles, 3 annexes, 32 tables, 15 figures, 3 implementing acts, the statement regarding the assumption of responsibility, and the author's CV.

1. RESEARCH METHODOLOGY

1.1 General characteristic of the research and design of the sample volume

The research project was realized the IMSP Institute of Cardiology and the Multipurpose Hospital „ NovaMed", on 110 admitted patients with acute myocardial infarction with ST-segment elevation (STEMI) exposed to coronary angioplasty. In order to achieve the goal and objectives, the study was divided in two parts, a prospective observational clinical cohort study and an experimental study.

The hypothesis of this study derives from the entity of the evidentiary material obtained in the retrospective clinical study conducted in our laboratory previously, which highlighted the markers of inflammation of the acute phase of myocardial infarction with predictive value on the pattern of post-myocardial infarction remodeling [13]. Applying the inclusion /exclusion criteria, 110 patients were selected. The study groups were formed depending on the development of the myocardial remodeling pattern, assessed at 6 months post-infarction, according to echocardiographic criteria. Group I consisted of 55 patients with adaptive myocardial remodeling (AMR); group II, 55 patients with pathological myocardial remodeling (RPM). A group of 20 healthy people was also formed, which served as a control group. The inclusion criteria were: patients over 18 years of age with acute STEMI, according to the 4th universal definition of myocardial infarction in 2018 [14]; primary revascularization in the first 12 hours after the onset of MI by coronary angioplasty with stent implantation; artery responsible for heart attack – left anterior descending artery (LAD). Exclusion criteria: repeated MI; non ST segment elevation MI; unstable angina; previously stented or intrastent restenosis; active liver disease; renal impairment with creatinine> 130 mcmol/l; severe diseases of the gastrointestinal tract; advanced heart failure (FE <30%); identifiable source of inflammation (systemic diseases, acute bacterial and viral infections or those taking long-term treatment with corticosteroids, anti-inflammatory drugs or immunosuppressants);

According to the first objective, the daily content of the main pro-inflammatory markers (IL-1, IL-6, TNF-α, MCP-1 and hcPCR) in the acute phase of the infarction (first 7 days) by ELISA method were determined, thus highlighting the role of the inflammatory response triggered by myocardial necrosis in the prediction of the remodeling pattern. The evaluation of the dynamic of the main anti-inflammatory markers (IL-α receptor antagonist (AR-IL-α), IL-4, IL-10, IL-33 and heregulin-1β) aimed to estimate the feasibility of the anti-inflammatory genetic program in the onset of the inflammatory response in the necrotized myocardium, the ratio of pro- / anti-inflammatory markers, as well as their predictive value regarding the pattern of development of post-infarction remodeling of the myocardium.

The pattern of post-infarction myocardial remodeling (adaptive or pathological) is closely related to the process of synthesis of type I and type III fibrillar collagen, triggered by the acute inflammatory response to the infarction, influenced respectively, by the ratio of pro-inflammatory cytokines/ anti-inflammatory and orchestrated by extracellular matrix metalloproteinases (MMP).

At this point, we determined the serum content of the type III collagen turnover markers at a distance of 1 month and of type III collagen markers at a distance of 3 months from the moment of myocardial revascularization, by ELISA method (figure 1). Synthesis markers of type I and type III collagen: PICP and PIIICP (carboxy segment of the collagen propeptide), respectively. Type I and type III collagen degradation markers: CITP and CIIITP, respectively (the carboxy segment of the telopeptide detached from the collagen peptide under the action of collagenases, ie, MMP-2 and MMP-8). The collagen turnover markers of the control group were estimated as reference indices, with which the indices from the 2 groups of patients with STEMI were compared.

At a distance of 6 months from the time of myocardial revascularization, echocardiographic indices were assessed in these 2 groups, including those accepted as landmarks for assessing the pattern of myocardial remodeling. Increase by more than 20% compared to the intake value of LV end-diastolic volume or LV end-sistolic volume, served as the criteria for pathological remodeling of the myocardium.

A part of clinical research was realized in the Central Laboratory of State University of Medicine and Pharmacy „Nicolae Testemitanu" (eg, serum level of pro- and anti-inflammatory markers on 1- and 3-months distance from revascularization). Another part was realized in the laboratory of Phillips University, Marburg, Germany (eg, serum level of markers inherent to type I and type III collagen synthesis as well as type I and type III collagen degradation, collagenase A and collagenase B on 1- and 3-months distance from revascularization).

The experimental study embraced 49 laboratory animals (white rats, *ratta albicans*), used for experimental model of isoproterenolic infarction reproduction. A part of research was realized in the laboratory of Interventional Cardiology of Institute of Cardiology (eg, isolated working heart perfusion), and another part in the laboratory of fundamental investigations „Max Delbrück", Berlin (eg, isovolumic heart perfusion).

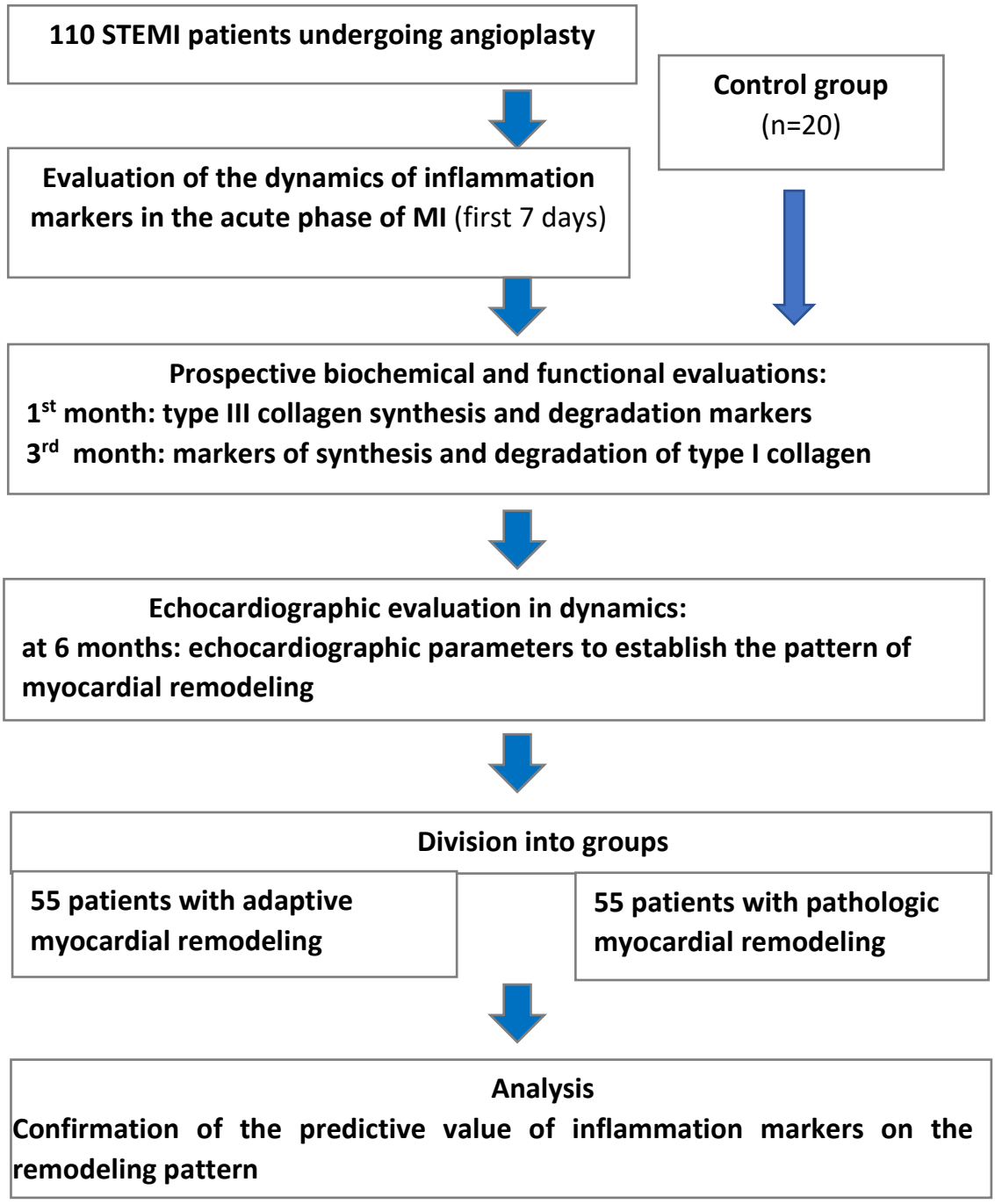

Figure 1. Design of the prospective observational cohort clinical study

1.2. Experimental study

The study was performed on white laboratory rats, maintained in the *ad libitum* regime, in which the model of experimental myocardial infarction (EMI) was reproduced by administering intraperitoneally two doses of isoproterenol (150 mg/kg) at a distance of 24 hours (the classic model of isoproterenolic infarction). The group with EMI consisted of 9 rats.

In 2 other study groups, the effect of the anti-inflammatory treatment performed by intraperitoneal administration was estimated: 1. TNF-α antagonist (am-TNF-α) at a dose of 50 mg/kg (IME + am-TNF-α group) for 7 days after 24 hours from the last isoproterenol injection (n = 9). 2. IL-10 at a dose of 50 mkg/kg (IME + IL-10 group) for 7 days after 24 hours after the last isoproterenol injection (n = 9). Rats that did not receive the mentioned medications served as the control group (n = 9).

The experiments were performed on the isovolumic isolated heart infusion model according to the Langendorff method [15] or in external working mode according to the Neely-Rovetto method [16], which allows the evaluation of the effort reactivity of the heart as well as the reactivity of the coronary system, by the Gregg coronary phenomenon and the Vanhoutte coronary phenomenon (Figure 2). Functional indices of the left ventricle were recorded via the Bio-Shell (Australia) real-time parameter monitoring device and computer-fixed in the experimental protocol.

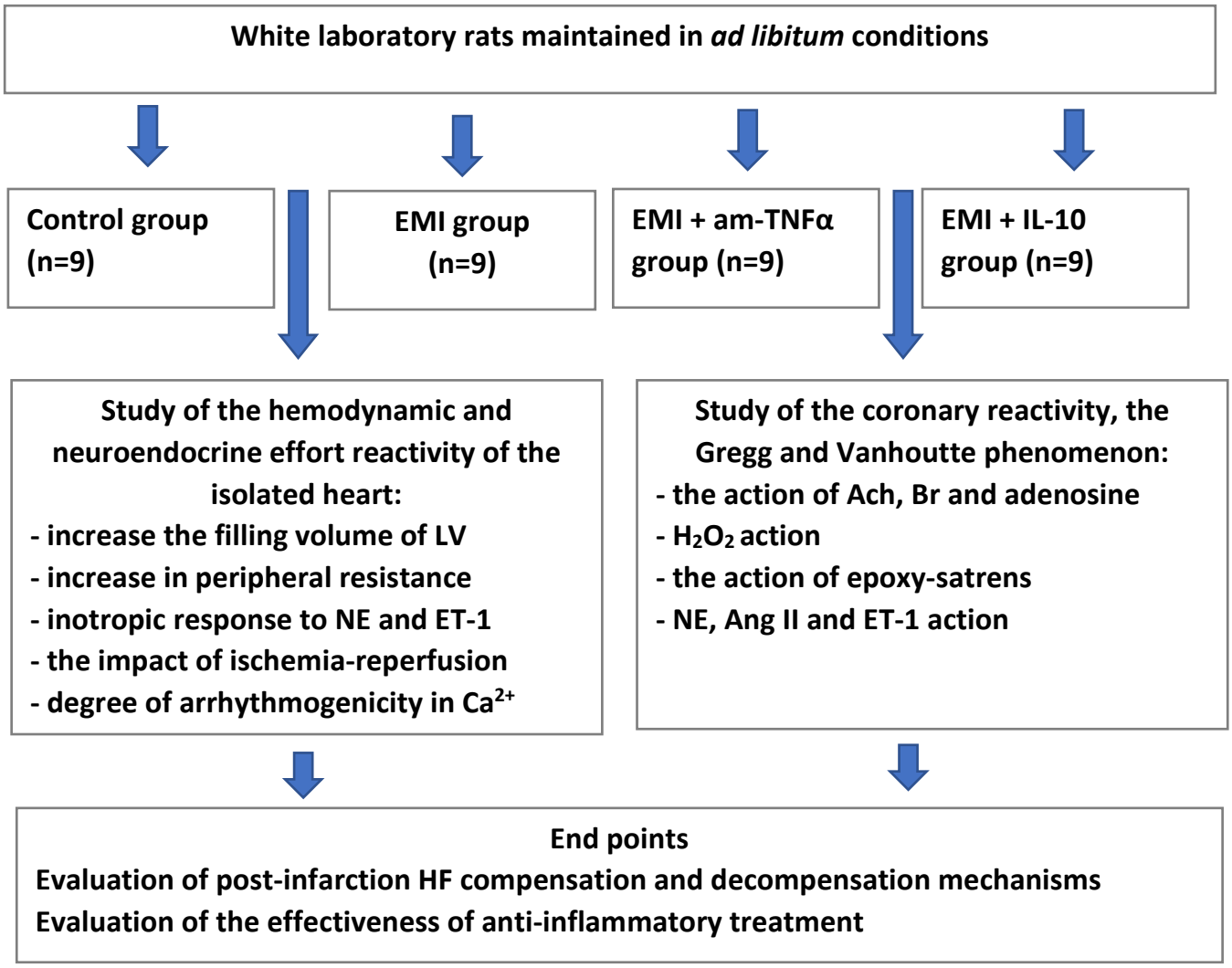

Figure 2. Design of the experimental study

Ethical considerations. The study was performed considering the international norms of medical ethics, established by the Helsinki Declaration, in terms of maintaining the confidentiality of participants' personal data. The research protocol received the approval from the Ethical Research Committee of the State University of Medicine and Pharmacy "Nicolae Testemitanu" (protocol no. 57, dated 29/04/2020, President of the committee C- Prof. Vovc Victor).

Statistical analysis. The statistical processing was performed using the Microsoft Excel program (Statistics). The data obtained were calculated using descriptive statistics (median, interquartile range deviation, minimum and maximum, standard deviation), the extremes were identified by estimating the "z" scores. Nonparametric tests were applied for multiple comparisons, depending on the number of evaluated groups. The Chi square test was applied to some nominal

variables. The estimation of the effect size was assessed by the "statistical significance". The graphic representation of the material was performed by constructing box-plot graphics, bar charts, line charts and pie charts.

2. CHAPTERS` SYNTHESIS

2.1. Clinical feature of STEMI patients

According to the inclusion and exclusion criteria, 110 patients were selected. Depending on the type of cardiac remodeling, the patients were divided into 2 groups: those with adaptive myocardial remodeling and those with pathological myocardial remodeling. The mean age of the patients in both groups was not significantly different, being 60.23 ± 1.42 in the AM group and 62.74 ± 1.58 in the PMR group (> 0.05). In both groups, men predominated in a quantity higher than 80% (> 0.05).

It was observed, when determining the anthropometric indices, that the average values between the studied groups are placed at the limit between the overweight group with high risk and high risk obesity, differing only by two units (28.44 ± 0.54 vs 30.09 ± 0 , 69 kg / m2,> 0.05). When analyzing the ratio of patients with diabetes, no differences were observed between the studied groups: in group I were detected 29.1% (16) patients and 27.3% (15) subjects in group II, (> 0.05). Most cardiovascular risk factors were estimated in a similar proportion in both cases, 9.1% in the first group and 7.3% in the second group (> 0.05). The status of current smoker, lightly but insignificant, differs between groups being 23.6% (13) and 14.5% (8), respectively (> 0.05). At admission 99.1% (109) patients presented with angina or retrosternal discomfort. The same percentage of subjects mentioned increased fatigue. Dyspnoea was present in 66.4%. Palpitations and nausea were less common in 6.4%, and syncope was described in 2 subjects. The assessment of the severity of heart failure in relation to MI, was estimated according to the Killip classification, 47.3% (52) at presentation showed signs of moderate heart failure, pulmonary congestion, 40% (44) had no clinical signs of heart decompensation and the remaining about 13 % were hospitalized with severe heart failure (Killip class III or IV).

2.2. Characteristic between groups by comparison of biochemical parameters in the first stage of the study

Upon presentation, the level of biomarker of myocardial necrosis, quantitative troponin, was statistically significantly higher in the PMR group vs. the AMR group, 17.06 ± 5.35 ng/ml vs. 9.46 ± 3.44 ng/ml, respectively (p <0.05). The CK-MB value was also significantly higher in the group of patients with PMR compared to those with AMR, 83.34 ± 16.24 U/L vs 48.15 ± 8.10U/L respectively (p <0.05) (Tab 6). Inflammatory status markers at first presentation did not show significant differences between groups. The mean creatinine value was also close in the two groups 101.23 ± 10.8 mcmol/l in the first group and 95.54 ± 3.31 mcmol/l in the second group (p> 0.05). The evaluation of the lipid spectrum, showed that at the initial stage LDL cholesterol values did not differentiate between groups being 3.0 ± 0.15 in group I and 3.18 ± 0.12 in group II (p > 0.05).

2.3. The characteristic of echocardiographic parameters by groups

The analysis of echocardiographic indicators at the initial stage showed homogeneity between the two groups studied. The sizes of the ascending aorta were insignificantly increased in the group of patients with PMR 35.00 ± 0.59 mm compared to the AMR group 33.00 ± 0.59 mm ($p < 0.05$). The mean values of the end-systolic and end-diastolic diameters of the left ventricle were similar in both samples ($p > 0.05$). The left ventricular end-diastolic volume was slightly different in group I 146.29 ± 4.90 ml compared to group II 129.87 ± 4.47 ml ($p < 0.05$), while the mean value of end-systolic volume in the left ventricle varied insignificantly in the 2 groups 76.82 ± 4.25 ml and 70.50 ± 4.07 ml ($p > 0.05$), respectively. The ejection fraction, similarly, at hospitalization balanced around the same average in both AMR group and PMR group ($p > 0.05$).

2.4. Evaluation of the dynamic of pro-inflammatory markers in the acute phase of infarction in STEMI patients who developed the adaptive or pathological pattern of post-myocardial infarction remodeling

Circulating levels of IL-1 and IL-6 in the acute phase of MI do not differ significantly in the groups of STEMI patients who developed AMR or PMR (Table 1).

Table 1. Serum levels of IL-1 and IL-6 in STEMI patients in the acute phase of infarction

Cytokine	Time	Control (n=20)	AMR (n=55)	PMR (n=55)
IL-1, pg/ml	Admission	5,13±0,6	6,87±0,6&	6,83±0,5&
	1 day		7,86±0,7*&	7,93±0,8*&
	2 day		8,86±0,6*&	8,93±0,7*&
	3 day		8,97±0,6*&	8,95±0,6*&
	4 day		8,14±0,9*&	8,24±0,8*&
	5 day		7,65±0,8*&	7,75±0,9*&
	6 day		6,96±0,9&	6,92±0,6&
	7 day		6,68±0,5&	6,71±0,8&
IL-6, pg/ml	Admission	4,84±0,5	6,56±0,6&	6,68±0,7&
	1 day		7,04±0,9&	7,14±0,8&
	2 day		8,23±0,9*&	8,39±0,9*&
	3 day		8,87±0,8*&	8,94±0,7*&
	4 day		8,11±0,8*&	8,19±0,9*&
	5 day		7,21±0,8*&	7,19±0,9*&
	6 day		6,87±0,8&	6,83±0,9&
	7 day		6,48±0,9&	6,56±0,8&

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling; & - significant ($p < 0.05$) versus control; * - significant ($p < 0.05$) versus admission

Worth mentioning that already at admission the serum content of IL-1 and IL-6 was significant in both groups above the control level (markers estimated in the group of healthy people, ie, the control group) by: 34% (IL-1, AMR), 33% (IL-1, PMR), 36% (IL-6, AMR) and 38% (IL-6, PMR). The increase in IL-1 and IL-6 was detected at day 3 of the acute phase of myocardial infarction, measuring the following similar relative elevation in groups: 30.5% (IL-1, RAM), 31.5% (IL-1, PMR), 36% (IL-6, RAM) and 34% (IL-6, PMR). Correspondingly, the

relative gap in the serum content of pro-inflammatory markers compared to the control level also became maximal on the 3rd day, as follows: 75% (IL-1, RAM), 76% (IL-1, PMR) , 84% (IL-6, RAM) and 85% (IL-6, PMR).

From the 4th day, in both groups of STEMI patients, was a progressive decline in circulating levels of IL-1 and IL-6 until the 7th day, when they practically reached the admission values.

The dynamic of the serum content of TNF-α in the acute phase of the infarction excelled through a common pattern in the dynamic of IL-1 and IL-6, namely the culmination of the circulating level on the 3rd day after the onset of STEMI (Table 2).

Table 2. Serum level of TNF-α in the acute phase of STEMI patients

Cytokine	Time	Control (n=20)	AMR (n=55)	PMR (n=55)
TNF-α, pg/ml	Admission	5,68±0,6	7,23±0,8&	7,35±0,9&
	1 day		7,63±0,7&	7,81±0,8&
	2 day		8,87±0,7*&	9,13±0,9*&
	3 day		9,64±0,9*&	9,83±0,9*&
	4 day		9,18±0,8*&	9,11±0,9*&
	5 day		8,78±0,9*	8,86±0,9*&
	6 day		8,14±0,8*&	8,26±0,9*&
	7 day		7,48±0,8&	7,52±0,9&

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling; & - significant (p <0.05) versus control; * - significant (p <0.05) versus admission

24 hours after the infarction, the serum admission content of TNF-α, which exceeded the control value by 28 and 30% in the groups of patients with AMR and PMR, respectively, increased insignificantly. On the 2nd day, the increase is significant in both groups and is 23% in the group of patients with AMR and 25% in the group of patients with PMR. The peak level of cytokine on the 3rd day was marked by an increase from the admission level of 34% in the group of patients with AMR and 35% in the group of patients with PMR. Similar to the dynamic of interleukins explored the serum TNF-α content is in both groups of patients is declining from day 4 to day 7, when it was established that the cytokine reached an insignificant difference versus the admission value: 7.48 ± 0.8 pg/ ml in patients with AMR and 7.52 ± 0.9 pg/ ml in patients with PMR.

Estimation of the dynamic of serum MCP-1 content in the acute phase of infarction revealed a significant elevation of cytokine in both groups later, compared to the admission level of IL-1, IL-6 and TNF-α (Table 3).

Table 3. Serum MCP-1 content in STEMI patients in the acute phase of infarction

Cytokine	Time	Control (n=55)	AMR (n=55)	PMR (n=55)
MCP-1, pg/ml	Admission	348,5±36	432,3±45&	444,5±46&
	1 day		457,6±48&	473,2±49&
	2 day		490,4±52&	493,8±54&
	3 day		549,6±58*&	558,7±57*&
	4 day		543,4±59*&	544,6±61*&
	5 day		527,8±62*&	533,2±58*&
	6 day		480,2±46&	488,4±51&
	7 day		447,5±45&	451,6±48&

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling; & - significant (p <0.05) versus control; * - significant (p <0.05) versus admission

The admission level of MCP-1 is practically equal in both groups and significantly exceeds the control value of the marker by an average of 28%. On the 3rd day, MCP-1 reaches the maximum circulating level for the acute phase of the infarction and is significant compared to the admission value, and the relative increase reaches levels of 28% for patients with AMR, as well as 26% for patients with PMR. Compared to the control marker, the MCP-1 gap at this period of the acute phase of the infarction is 58% in the RAM group and 61% in the PMR group. Similarly to the dynamic of IL-1, IL-6 and TNF-α in the acute phase of myocardial infarction, the serum content of MCP-1 is progressively depreciated, starting with the 4th day, and the imminent estimation of day 6 already indicates circulating levels of the marker without significant difference compared to the admission value. However, the serum content of MCP-1 on the 7th day remains significantly above the control value of the marker by 28-30%.

Remarkably, the serum level of hsCRP demonstrated a similar dynamic, with only one notable difference: the marker on day 7 remains significantly higher than the admission value (Table 4).

Table 4. Serum content of hsPCR-1 in STEMI patients in the acute phase of infarction

Cytokine	Time	Control (n=20)	AMR (n=55)	PMR (n=55)
hsCRP, mg/L	Admission	0,87±0,1	4,17±0,4&	4,22±0,4&
	1 day		4,58±0,5&	4,65±0,5&
	2 day		6,73±0,6*&	6,35±0,7*&
	3 day		8,92±0,9*&	9,23±0,8*&
	4 day		8,12±0,8*&	8,46±0,9*&
	5 day		7,39±0,7*&	7,84±0,8*&
	6 day		6,84±0,7*&	7,16±0,5*&
	7 day		6,20±0,7*&	6,58±0,8*&

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling; & - significant ($p < 0.05$) versus control; * - significant ($p < 0.05$) versus admission

The hsPCR level on the 2nd day demonstrated a conclusively significant elevation rate of 62% in patients with AMR and 51% in patients with PMR, which correlates with the significant increase in IL-1, IL-6 and TNF- α. On the 3rd day, the elevation in serum hsCRP content is greater than 100% in both groups (114% in patients with AMR and 119% in patients with PMR). The decrease in the circulating level of hsCRP from day 3 to day 7 is, compared to that attested for IL-1, IL-6 and TNF-α, much more reserved, thus, at the last estimation of the acute phase of the infarction it remains significant in both groups above the value by 50 and 56% in patients with AMR and PMR, respectively.

Therefore, neither hsCRP does not demonstrate in the acute phase of infarction notable differences between patients who developed adaptive post-infarct remodeling and patients who developed PMR. Therefore, the influences of pro-inflammatory markers in the acute phase of the infarction on the patterns of post-infarction remodeling of the myocardium are not determinative, and the markers do not have the predictive value in this regard.

2.5. Evaluation of the dynamic of anti-inflammatory markers in the acute phase of infarction in patients with STEMI who developed the adaptive or pathological pattern of post-myocardial infarction remodeling

The evaluation of the dynamic of the serum content of the main anti-inflammatory markers in STEMI patients in the acute phase of the infarction aimed to estimate the feasibility of the anti-inflammatory genetic program in triggering the inflammatory response in the necrotized myocardium, the ratio of pro-/anti-inflammatory markers, as well as their predictive value *vis-à-vis* the developmental pattern of post-myocardial infarction remodeling. The admission value of the anti-inflammatory marker antagonist receptor of the IL-1α (AR-IL-1α) does not differ significantly from the control value (Table 5).

Table 5. Serum content of AR-IL-1α in patients with STEMI in the acute phase of infarction

Cytokine	Time	Control (n=20)	AMR (n=55)	PMR (n=55)
AR-IL-1α, pg/ml	Admission	5,78±0,5	5,33±0,6	5,37±0,7
	1 day		5,25±0,7	5,21±0,8
	2 day		5,14±0,6	5,17±0,5
	3 day		4,72±0,5&*	4,79±0,6&*
	4 day		4,96±0,6	4,93±0,7
	5 day		5,22±0,8	5,11±0,7
	6 day		5,30±0,9	5,27±0,8
	7 day		5,45±0,8	5,38±0,7

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling; & - significant ($p < 0.05$) versus control; * - significant ($p < 0.05$) versus admission

In the first 3 days of the acute phase of infarction, a decrease of AR-IL was observed, so that on the 3rd day the lowest circulating level of the marker was observed in both groups: 4.72 ± 0.5 pg/ ml for AMR and 4.79 ± 0.6 pg/ ml for PMR. Starting on day 4, there was a tendency to increase the circulating level of AR-IL-1α, so that on the 7th day the serum content of the marker reached the control level in both groups (5.78 ± 0, 5 pg/ml) and the level of admission without significant discrepancy.

The growth rate of AR-IL-1 from day 3 to day 7 in patients who developed AMR was 16% (from 4.72 ± 0.5 to 5.45 ± 0.8 pg/ ml). In patients who developed PMR, the growth rate of AR-IL-1α was similar and was 13% (from 4.79 ± 0.6 to 5.38 ± 0.7 pg/ ml). The quantitative values of AR-IL-1α do not differ between groups even during the acute phase of the infarction, when the inflammatory response is marked by the expression of anti-inflammatory macrophages, M2. Therefore, the anti-inflammatory marker, AR-IL-1α, estimated in the acute phase of infarction has no predictive value on the pattern of development of post-infarction myocardial remodeling in STEMI patients.

The IL-4 dynamic, common for both groups, was the significant decrease at similar levels of the admission value of the content of the anti-inflammatory marker compared to the control level by an average of 19% (Table 6).

Table 6. Serum IL-4 content in STEMI patients in the acute phase of infarction

Cytokine	Time	Control (n=20)	AMR (n=55)	PMR (n=55)
IL-4, pg/ml	Admission	4,88±0,6	3,91±0,4&	3,93±0,4&
	1 day		3,84±0,4&	3,80±0,5&
	2 day		3,79±0,5&	3,73±0,5&
	3 day		3,74±0,4&	3,71±0,3&
	4 day		4,21±0,4&	3,85±0,5&
	5 day		4,73±0,5* p<0,05	3,88±0,4&
	6 day		4,94±0,5* p<0,05	3,82±0,4&
	7 day		5,73±0,6* p<0,05	3,92±0,5&

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling
& - significant (p <0.05) versus control; * - significant (p <0.05) versus admission; p - the significance of the discrepancy vs PMR

The distinction of IL-4 dynamic was detected after the 3rd day of the acute phase of the infarction. Its entity consists in the fact that in the group of patients, who developed adaptive post-infarct remodeling of the myocardium, the circulating level of IL-4 increased markedly and progressively starting from the 4th day, reaching on the 7th day a growth rate of 54% compared to the minimum value imminent on the 3rd day. Moreover, already on the 5th day the circulating level of IL-4 significantly exceeds the admission value and does not differ significantly from the control value.

In the group of patients who developed post-myocardial infarction remodeling, the circulating level of IL-4 increased after the 3rd day to the 7th day by only 6%: from 3.71 ± 0.3 to 3.92 ± 0.5 pg/ ml. In terms of this pattern of dynamic, the serum IL-4 content in patients with AMR becomes significantly higher compared to the marker in the group of patients with PMR: by 22% on the 5th day, by 30% on the 6th day, and with 47% on the 7th day.

Therefore, IL-4 can be estimated as an anti-inflammatory marker with predictive value for the pattern of development of post-myocardial infarction remodeling, so that its elevation of circulating level by more than 50% in the period from the 3rd day to the 7th day of the acute phase of the infarction, AMR is imminent, and in the case of an average growth rate of 6%, the risk of developing PMR is predicted.

It is important to note that in addition to the similarities of IL-4 and IL-10 in the pathogenetic interface of the control and regulation of the inflammatory response, the results of our study also showed a similar dynamic of these 2 anti-inflammatory interleukins in the acute phase of myocardial infarction in patients with STEMI (Table 7).

Table 7. Serum IL-10 content in STEMI patients in the acute phase of infarction

Cytokine	Time	Control (n=20)	AMR (n=55)	PMR (n=55)
IL-10, pg/ml	Admission	6,92±0,7	5,12±0,6&	5,16±0,5&
	1 day		5,24±0,4&	5,21±0,4&
	2 day		5,16±0,6&	5,20±0,5&
	3 day		4,85±0,4&	4,83±0,4&
	4 day		5,78±0,6&	4,76±0,5&
	5 day		6,26±0,7* p<0,05	4,85±0,5&
	6 day		6,98±0,7* p<0,05	5,08±0,6&
	7 day		7,53±0,8* p<0,05	5,11±0,5&

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling
& - significant (p <0.05) versus control; * - significant (p <0.05) versus admission; p - the significance of the discrepancy vs PMR

The dynamic of IL-10 is similar to that of IL-4 in the acute phase of myocardial infarction (Table 7). At admission the circulating level of IL-10 is practically equal in both groups and significantly depreciated to the control value on average by 26%, on the 3rd day the serum content of IL-10 does not differ significantly from the admission value. The dynamic of IL-10 after the 3rd day is notably different in groups. There was a marked elevation of IL-10 in the AMR group from the 3rd day to the 7rd day by 56%, so a growth rate practically equal to that attested in the dynamic of the circulating level of IL-4: 56 vs 54%.

Due to this considerable elevation, the circulating level of IL-10 becomes significantly higher compared to the level of admission to the estimates of the 5th, 6th and 7th days of the acute phase of the infarction and, similar to IL-4, does not really differ from the control value.

The serum content of IL-10 in patients with AMR becomes, as in the case of IL-4 evaluation, significantly higher compared to the marker in the PMR group, the attested gap being even larger compared to the imminent IL -4: 29% on the 5th day, 38% on the 6th day and 48% on the 7th day.

Therefore, IL-10 also has predictive value on the pattern of post-myocardial infarction remodeling in STEMI patients, so that its elevation of circulating level by more than 50% in the period from the 3rd to the 7rd day of the acute phase of the infarction is related to AMR, and in the case of an average growth rate of 6%, predictably the risk of developing PMR is announced.

2.6. Evaluation of inflammation markers in STEMI patients, echocardiographic parameters, and extracellular matrix remodeling markers at a distance of 1, and 3 months after angioplasty in relation to the imminent prediction of IL-4 and IL-10 dynamic

The predictive relevance of the change in the serum levels of IL-4 and IL-10 during the repolarization of macrophages (day 4 - day 7) in the acute phase of infarction was verified, to predict the development of adaptive or pathological post-infarction remodeling in patients with STEMI subjected to angioplasty.

At 6 months post-MI (the period of completion of the post-myocardial infarction remodeling) the nature of the echocardiographic change compared to the admission value of LVESD, LVEDV, EF and others was evaluated. The increase of the value of LVESV or LVEDV by more than 20% indicates a pathological remodeling of the myocardium. The insignificant increase or decrease of their value represents an echocardiographic signal of the adaptive post-

infarct remodeling of the myocardium. According to these criteria, 2 groups of patients were formed: 1) Patients with AMR (n = 55), with end-systolic and/or end-diastolic volumes of LV increased up to 20% compared to baseline; 2) Patients at risk of developing PMR (n = 55), with end-systolic and/or end-diastolic volumes of LV increased by 20% and more, compared to the initial value. The results that conclusively confirm the predictive value of IL-4 and IL-10 regarding the pattern of post-myocardial remodeling in patients with STEMI are shown in the following table (Table 8).

Table 8. Dynamic of echocardiographic parameters in patients with STEMI

Parameter	AMR (n=55)	PMR (n=55)
Rate of serum IL-4 elevation in the acute phase	53,6±6,8%	5,7±5,2%
Rate of serum IL-10 elevation in the acute phase	54,1±6,9%	5,5±4,9%
LV end-diastolic diameter, mm Initial (M±SD) Initial (Median) [P25-P75] 6 months (M±SD) Initial (Median) [P25-P75]	 54,07±0,82 53,4 [51,3-57,8] 54,12±0,75 52 [50,2-55]	 52,36±0,82 51 [49-53,4] 59,09±0,95 (+11%) 57 [53,7-61,25]
LV end-systolic volume, ml Initial (M±SD) Initial (Median) [P25-P75] 6 months (M±SD) Initial (Median) [P25-P75]	 76,82±4,25 73 [56-94] 74,88±4,71 (-3%) 75 [59-91]	 70,5±4,07 70 [51,5-98] 106,35±5,58 (+50%) 104 [80-112] p=0,00254 vs RAM
LV end-diastolic volume, ml Initial (M±SD) Initial (Median) [P25-P75] 6 months (M±SD) Initial (Median) [P25-P75]	 146,29±4,90 150 [174-166] 147,58±5,024 151 [134-169,7]	 129,87±4,47 138 [111,3-165,8] 188,94±6,09 (+45%) 190 [176-208] p=0,00281 vs RAM

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling

Indeed, STEMI patients who showed worsening echocardiographic parameters (increase of LV end-systolic volume and LV end-diastolic volume compared to the initial value by 50% and 45%, respectively, as well as the decrease of FE by 7%) 6 months after the procedure and developed PMR, had very modest modification of IL-4 and IL-10 (5.7% and 5.5%) during the acute phase of the infarction.

On the other hand, patients who showed an improvement of echocardiographic parameters (with the LV end-systolic volume and LV end-diastolic volume having a decreasing tendency and the ejection fraction increasing by 8%) 6 months after the procedure and developed AMR, had a more than 50% increase of IL-4 and IL-10 levels during the acute phase of infarction.

The estimation of pro-inflammatory markers at a distance of 1 and 3 months did not detect any noticeable differences between the AMR and PMR pattern (Table 9).

Table 9. Serum content of pro-inflammatory markers in patients with STEMI at 1 and 3 months after angioplasty

Marker	AMR (n=55)		PMR (n=55)	
	1 month	3 months	1 lună	1 month
IL-1 (M±SD) ME [P25-P75]	5,26±0,6 5,1 [4,9-5,3]	5,19±0,6 5,3 [5,10-5,52]	5,32±0,6 5,37 [5,29-5,45]	5,21±0,6 5,1 [4,9-5,3]
IL-6 ME [P25-P75]	6,18±0,5* 6,71 [5,9-6,34]	5,75±0,5* 5,7 [5,65-5,92]	6,29±0,5* 6,26 [6,12-6,37]	5,83±0,5* 5,83 [5,74-5,96]
TNF-α ME [P25-P75]	7,23±0,7* 7,28 [7,21-7,38]	6,56±0,6* 6,49 [6,3-6,67]	7,44±0,8* 7,46 [7,36-7,54]	6,85±0,7* 6,86 [6,74-6,94]
MCP-1 ME [P25-P75]	416,4±39* 411 [400-422]	367,7±32 364 [344-379]	424,4±41* 421 [408-427]	378,4±42 375 [373-388]
hsPCR ME [P25-P75]	5,1±0,6** 5,11 [4,95-5,19]	4,3±0,5** 4,29 [4,19-5,35]	5,8±0,7** 5,88 [5,79-5,98]	4,8±0,6** 4,89 [4,78-4,96]

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling ME- median; P25 și P75 – percentile 25% și 75%; * p<0,01 vs control * p<0,01 vs control * - significant (p<0,05) versus the control marker; ** - significant (p<0,001) versus the control marker

The estimation of anti-inflammatory markers at a distance of 1 and 3 months did detect a noticeable difference between the AMR and PMR pattern only for IL-4 and IL-10 (Table 10).

Table 10. Serum content of anti- inflammatory markers in patients with STEMI at 1 and 3 months after angioplasty

Marker	AMR (n=55)		PMR (n=55)	
	1 month	3 months	1 month	3 months
AR-IL-1α ME [P25-P75]	5,89±0,6 5,87 [5,75-5,86]	5,61±0,5 5,64[5,61-5,82]	5,79±0,5 5,8 [5,77-5,85]	5,68±0,6 5,66 [5,53-5,79]
IL-4 ME [P25-P75]	5,21±0,6 5,22 [5,12-5,29]	4,95±0,5 4,97[4,88-5,14]	4,08±0,4* 4,12 [3,92-4,22] p=0,00321	4,19±0,4* 4,22 [4,11-4,27] p=0,00182
IL-10 ME [P25-P75]	7,08±0,7 7,04 [6,94-7,21]	6,89±0,6 6,85[6,79-6,95]	5,83±0,6* 5,88 [5,79-5,95] p=0,00574	6,11±0,7* 6,19 [5,98-6,26] p=0,00756
IL-33 ME [P25-P75]	3,83±0,3 3,81 [3,76-3,89]	3,91±0,3 3,94[3,85-4,06]	3,64±0,3 3,66 [3,59-3,69]	3,81±0,3 3,83 [3,75-3,91]
Heregulina-1β ME [P25-P75]	5,17±0,5 5,14 [5,07-5,20]	5,47±0,4 5,45[5,39-5,52]	5,07±0,5 5,08 [5,05-5,13]	5,33±0,5 5,31 [5,28-5,41]

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling ME- median; P25 și P75 – percentile 25% și 75%; * p<0,01 vs control * p<0,01 vs control * -

significant (p<0,05) versus the control marker; ** - significant (p<0,001) versus the control marker; p – significance vs AMR

Regarding the serum content of pro- and anti-inflammatory markers at a distance of 1 and 3 months, the following features are important:

1. The circulating level of hsCRP in both groups remains above the critical value of 3.0 mg/L, both at a distance of 1 and 3 months.
2. The circulating level of IL-1 has decreased in both groups to the values of the control group already after 1 month and remains within the permissible error and at a distance of 3 months.
3. The circulating level of IL-6 and TNF-α is significantly increased compared to the control markers in both groups of patients at both cases 1 and 3 months, with no significant difference between groups.
4. The serum content of the chemokine MCP-1 is found to be significantly increased in both groups only at a distance of 1 month. After 3 months the marker decreases to values without significant difference from the control value.
5. Anti-inflammatory markers, which have no predictive value on the pattern of post-myocardial infarction remodeling (ie, AR-IL-1a, IL-33 and heregulin-1β) were imposed by imminent circulating levels on control markers in both groups, both at a distance of 1 and 3 months.
6. The serum content of IL-4 and IL-10 remains significantly underlying the control value only in the group of patients with PMR, both at a distance of 1 month and after 3 months from the time of angioplasty.
7. No significant differences in inflammation markers were found between the groups of patients with AMR and PMR at a distance of 1 and 3 months post-infarction, with the exception of IL-4 and IL-10. In PMR, the serum content of IL-4 is below the AMR level by 21.7% at a distance of 1 month and 15.36% at a distance of 3 months. The IL-10 recoil is 17.66% at a distance of 1 month and 11.32% at a distance of 3 months after angioplasty.

The post-infarction period of 1 month is conceptually required by completing the synthesis of type 3 collagen. The feasibility of this process depends on the activity of fibroblasts and myofibroblasts, as well as the activity of collagenase A (MMP-1) which has proteolytic properties compared to this fibrillar collagen. We determined in both groups the serum content of MMP-1 at a distance of 1 month of post-infarction evolution in correlation with the markers of synthesis and degradation of type III collagen (table 11).

Table 11. Serum content of MMP-1, PIIICP and CIIITP in patients with STEMI after 1 month

Marker	Control (n=20)	AMR (n=55)	PMR (n=55)
MMP-1 (µg/ml) ME [P25-P75]	4,5±0,5 4,48 [4,41-4,49]	5,1±0,5 4,95 [4,9-5,3]	8,8±0,8* 8,85 [8,5-9,2] p=0,00214 vs RAM
PIIICP (ng/ml) ME [P25-P75]	7,2±0,6 7,19 [7,15-7,28]	14,1±1,3* 14,2 [13,9-14,2]	13,9±1,3* 13,9 [13,7-14,2] p=0,05588 vs RAM
CIIITP (ng/ml) ME [P25-P75]	5,8±0,5 5,77 [5,73-5,84]	6,1±0,6 5,95 [5,7-6,25]	11,4±1,2* 11,45 [10,7-11,5] p=0,00182 vs RAM

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling ME- median; MMP-1 – metalloproteinase 1; PIIICP - Procollagen III C-Terminal Propeptide; CIIITP - Collagen III Carboxy-Telopeptide; P25 și P75 – percentile 25% și 75%; * p<0,01 vs control * p<0,01 vs control

Regarding the turnover of type III fibrillar collagen estimated at a distance of 1 month, is important to mention the significant increase of the circulating level of the degradation marker, CIIITP by 97% compared to the control marker in the group of patients with PMR. In support of this important evidence, a significant increase in the circulating level of collagenase A is announced, which preferentially cleaves type III collagen (ie, MMP-1) by 96%.

If the type III fibrillar collagen synthesis marker (PIIICP) increases significantly in both groups by 96% in AMR and 93% in PMR compared to the control marker, then significant changes in MMP-1 and CIIITP in the group of patients with AMR were not found.

Remarkably, similar changes in ECM markers are also detected 3 months after angioplasty (Table 12).

Table 12. Serum content of MMP-1, PICP and CITP in patients with STEMI at a distance of 3 months

Marker	Control (n=20)	AMR (n=55)	PMR (n=55)
MMP-8 (µg/ml) ME [P25-P75]	8,7±0,8 11,45 [10,7-11,5]	8,2±0,8 8,25 [10,7-11,5]	15,5±1,3* 15,60 [14,92-15,5] p=0,00042 vs RAM
PICP (ng/ml) ME [P25-P75]	12,3±1,8 12,26 [12,23-12,34]	18,3±1,8* 18,25 [18,2-18,38]	17,9±1,3* 18,00 [17,65-18,2] p=0,0595 vs RAM
CITP (ng/ml) ME [P25-P75]	14,6±1,5 14,5 [14,4-14,61]	15,2±0,6 15,16 [15,11-15,25]	23,4±2,4* 23,35 [22,8-23,5] p=0,00091 vs RAM

Note: AMR – adaptive myocardium remodeling; PMR – pathological myocardium remodeling; MMP-8 – metalloproteinase 8; PICP - Procollagen I C-Terminal Propeptide; CITP - Collagen I Carboxy-Telopeptide; ME- median; P25 și P75 – percentile 25% și 75%; * p<0,01 vs control

Similarly, to the type III collagen, the circulating level of the type I collagen synthesis marker is at a distance of 3 months significantly higher with 49% in AMR and 46% in PMR compared to the control marker, understandable associated phenomenon with significantly increased values of IL-6, TNF-α and hsCRP at this period of post-infarction progression. This evidence is consistent with the current concept of post-infarction myocardial remodeling that strengthens the marked profibrotic effect of these pro-inflammatory cytokines.

Patients who developed adaptive post-infarct remodeling of the myocardium had normal values of MMP-1 and CITP at a distance of 3 months. This phenomenon is in agreement with the normal circulating levels of IL-4 and IL-10 at a distance of 3 months. In contrast, in patients with PMR the serum content of these anti-inflammatory interleukins is significantly reduced compared to the control value.

Therefore, the dynamic evaluation of the inflammatory response in patients with STEMI who develop AMR or PMR revealed the determinant value of IL-4 and IL-10. Anti-inflammatory cytokines with different content depending on the remodeling pattern, has a beneficial influence on the remodeling of the extracellular matrix and the quality of myocardial remodeling.

2.7. Experimental study

In the experimental myocardial infarction (EMI) classically induced by isoproterenol, the vulnerability of the left ventricular function (LV) has already been attested in the physiological infusion regime. Thus, the value of the parameters of the pump function, aortic jet (AJ), coronary flow (CF) and cardiac output (CO) was up to 30% lower than the control, and the developed systole pressure in the LV was only 65.3% of the control level. Characteristic for EMI was the diastole dysfunction, which was manifested by an increase of 84,1% end-diastolic pressure in LV and an increase of over 44% in diastolic stiffness (DS).

The adaptive capacity of the isolated heart in EMI was impaired compared to the control in various hemodynamic and neuroendocrine tests.

Thus, in conditions of minimal filling of the left atrium and 38% pressure increase in the aortic estuary, the decline in pump function indices became even higher than in the control, due to the worsening of the relaxation and isovolumic contraction of the heart (Table 13).

Table 13. Pump parameters of the isolated heart in hemodynamic effort with volume and resistance

Parameter	Control		EMI	
	Volume effort	Resistance effort	Volume effort	Resistance effort
Aortic jet, ml/min	5,7±0,45	2,3±0,22 -59,6% (p<0,001	16,8±1,7	7,3±0,7 -56,5% (p<0,001)
Coronary output, ml/min	16,2±1,4	9,6±0,85 -40,7% (p<0,001)	29,4±3,1	15,8±1,6 -46,3% (p<0,001)
-dP/dT max, mm Hg/sec	8206±172	6124±167 -25,4% (p<0,05)	8242±227	5665±226 -31,3% (p<0,05)
+dP/dT max, mm Hg/sec	6387±163	4836±147 -24,3% (p<0,05)	7196±219	5123±164 -28,8% (p<0,05)

Note: EMI – experimental myocardium infarction; -dP/dT max – velocity of isovolumic relaxation; +dP/dT max – velocity of isovolumic contraction

The aortic jet decreased by 59,6% in effort with minimal volume, and in effort with resistance the recoil from the control was 56,5%. The 30% impairment rate of cardiac output detected in the physiological infusion regime increased by 36% in effort with minimal volume and by 55% in effort with resistance. Remarkably, in these tests of hemodynamic effort increased the decline in the value of the maximum speed of relaxation and isovolumic contraction of the heart by up to 50% and up to 26%, respectively, which calls into question the role of these phases of the cardiac cycle in control and in affecting the hetero- and homeometric regulation of the heart. Another important part of the pathophysiology of heart failure caused by EMI is the negative

inotropic response of the heart to the action of ET-1, appreciated by the decrease of systolic pressure of the LV stimulation peak by 4,1%, associated with the reduction of CO by 12,5%. In the control group, the dynamic of these parameters reflected the positive inotropic effect of the heart on the ET-1 action: their increase by 17,7% and 16,8%, respectively. The evolution of EMI excelled by affecting endothelial-mediated coronary reactivity (Table 14).

Table 14. Coronary functional reserve of the isolated isovolumic heart

Group	**Coronary function reserve (%) at the action of vasodilator stimuli (10-6M (10^{-6}M)**				
	Ach	**Br**	**Ad**	**H_2O_2**	**EPC**
Control	35,6±3,4	22,3±2,4	24,8±2,4	14,4±1,4	13,8±1,5
EMI	21,2±2,2 -40,4% vs control p<0,01	15,8±1,7 -29,1% vs control p<0,05	16,9±1,8 -31,8% vs control p<0,05	15,5±1,5 +7,6%	13,7±1,4

Note: EMI – experimental myocardium infarction; Ach – acetylcholine; Br – Bradykinin; Ad – adenosine; H_2O_2 – peroxide of hydrogen; EPC – epoxieicosatriens

Attenuation of inflammation in IME by administration of either am-TNF-α or IL-10 improved the cardiac function (Table 15).

Table 15. Functional indices of cardiac exertion at the action of am-TNF-α or IL-10

Group	**AJ (ml/min) in minimal volume**	**AJ (ml/min) in effort resistance**	**Systolic pressure of LV (mm Hg) action of ET-1**	**Coronary flow reserve (%) action of Ach**
Control (n=9)	5,7±0,45	16,8±1,7	170,3±10,4 +17,7% vs initial	35,6±3,4
IME (n=9)	2,3±0,22*	7,3±0,7*	91,7±9,2* -4,1% vs initial	21,2±2,2*
IME + am-TNF-α (n=9)	3,4±0,27* p<0,05	12,6±1,2* p<0,05	132,3±10,4* +10,8% vs initial p<0,05	27,8±2,6* p<0,05
IME + IL-10 (n=9)	3,7±0,25* p<0,05	12,9±1,1* p<0,05	134,5±10,2* +11,1% vs initial p<0,05	28,3±2,5* p<0,05

Note: EMI – experimental myocardium infarction; AJ – aortic jet; Ach – acetylcholine * - significant vs control (p <0.05); p - value of significance vs EMI

Thus, the AJ value in the effort with volume and resistance increased by up to 77% in the treatment groups, and the ET-1 action was imposed by the appearance of the positive inotropic effect. It is also important to increase by over 32% the coronary flow reserve under the action of acetylcholine, and on the other hand to reduce by over 23% the LV end-diastolic pressure at the impact with ischemia (attestation at min 30), as well as by over 25% in reperfusion (min 45).

This imminent functional reversal of both formulas of anti-inflammatory treatment indicates with certainty the role of inflammation in the evolution of post-infarction heart failure and basically reflects data obtained in the clinical study showing that the elevation of over 50% of

circulating levels of IL-4 and IL-10 in the acute phase of infarction in STEMI patients is related with adaptive myocardial remodeling. Due to its proved benefit, the TNF-α antagonist and IL-10 deserves an appropriate approach in the clinical management of STEMI.

CONCLUSIONS

1. Due to a similar dynamic of the main pro-inflammatory markers (PCRhs, IL-1, IL-6, TNF-α, MCP-1) estimated daily in the serum, in the acute phase of infarction in both groups of patients with adaptive and pathological remodeling, there is not any predictive value regarding the post-infarction remodeling pattern.

2. Among the explored anti-inflammatory makers, only the dynamic of IL-4 and IL-10 in the acute phase of infarction was markedly different between groups, the increased serum content of these interleukins from the 3rd day to the 7th day, over than 50% was imminent to the adaptive post-infarct remodeling of the myocardium, and their elevation less than 5% was characteristic for patients with the pathological pattern of remodeling, proving the predictive value on the post-infarction myocardial pattern of remodeling.

3. The inflammatory response in the acute phase of the infarction is correlated with the extracellular matrix remodeling markers. The elevation of IL-4 and IL-10 characteristic for patients with adaptive remodeling, is associated with normal circulating levels of type III (CIIITP) and type I (CITP) collagen degradation markers at a distance of 1 and 3 months, respectively. In pathological remodeling their serum content is significantly above the control value and therefore can be its predictor.

4. The experimental study provided important evidence on the mechanisms of exacerbation of heart failure in post-infarction myocardium, in hemodynamic and neuroendocrine exertion, as well as the estimated efficacy of anti-inflammatory treatment in isolated rat heart. Decreased rate of relaxation and isovolumic contraction of the heart up to 33.5%, negative inotropic response to ET-1 action, endothelium-dependent coronary heart disease Gregg are the main pathogenetic mechanisms of the progressive decline of the pump function of the left ventricle.

5. Attenuating the inflammation by administration of TNF-α antagonist (am-TNF-α) or IL-10 led to favorable functional changes of the heart, the main manifestations were the appearance of a positive inotropic response to the action of ET-1, increased coronary function reserve to the action of acetylcholine with up to 25% and the tolerance of the myocardium to the impact of ischemia-reperfusion, the increase of the arrhythmogenic threshold of the myocardium and the maintenance of the functional nativity of the Vanhoutte coronary phenomenon. At the same time, the functional benefit of EMI treatment with IL-10 confirms the clinical data, as well as its predictive value on the development of the adaptive post-infarction remodeling pattern of the myocardium.

6. Based on the results of the clinical and experimental study, an algorithm for the prediction of the pathological post-infarction myocardial remodeling pattern can be strengthened, the main elements are: (i) low increase in IL-4 and IL-10 in the acute phase of infarction , (ii) elevated serum levels of fibrillar collagen degradation markers type III and I at a distance of 1 and 3 months, respectively, (iii) an increase of more than 20% from baseline in VTDVS, VTSVS and DTDVS during - myocardial infarction;

PRACTICAL RECOMMENDATIONS

1. Estimating the dynamic of IL-4 and IL-10 in the acute phase of infarction in STEMI patients provides the predictive value on the pattern of post-infarction myocardial remodeling, so that its increase from the 3rd to the 7th day with over 50% indicates the prognosis of adaptive remodeling, and the increase in interleukins <5% - indicates the risk of pathological remodeling. In this context, it is announced that the post-infarction pharmacological treatment will be facilitated in terms of approaching the personalized or individual treatment.

2. The notable functional benefit of TNF-α antagonist (am-TNF-α) and IL-10 found in the experimental study with isoproterenolic infarction model justifies the plausibility of applying these anti-inflammatory remedies in the acute phase of infarction in STEMI patients, where inert dynamic of IL-4 and IL-10 predicts the risk of developing pathological post-myocardial infarction remodeling.

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