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Perforin Expression after Acute Myocardial Infarction – A Pilot Study

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A B S T R A C T

Perforin is an important mediator of inflammatory reactions. It is a quick-action cytotoxic mediator accumulated in the cytoplasmic granules of effector immunity cells (T lymphocytes, NK and NKT cells) which provide death signal in infected or transformed cells. Perforin-positive cells were previously detected in myocardial tissue during Trypanosoma cruzi infection and viral myocarditis while its role in chronic and progressive cardiovascular inflammatory disease such as atherosclerosis is almost completely unexplored. The perforin activity is also untested during acute coronary events that represent unexpected atherosclerotic complications due to the inflammatory destabilisation and atherosclerotic plaque rupture. The aim of this study was to investigate the presence of perforin, an important immunological inflammatory molecule in peripheral blood lymphocytes during the early period after acute myocardial infarction. We analyzed three subject groups: women with ST-segment elevation acute myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI), conservatively treated women with acute myocardial infarction without ST-segment elevation (NSTEMI) and a control group of healthy volunteers. The STEMI and NSTEMI groups did not basically differ in medication neither in levels of routine laboratory tests, while troponin I were significantly higher in the STEMI group. In the study, we detected an early decrease of perforin-positive lymphocytes in STEMI patients that were in contrast with their persisting elevation among NSTEMI patients. Despite greater myocardial necrosis in the STEMI group, results of this pilot-study indicated the prolonged perforin-mediated inflammatory response in patients with NSTEMI. This perforin down-regulation that follows the coronary interventional reperfusion in STEMI emphasized the possible anti-inflammatory role of primary PCI among patients with acute myocardial infarction. Given that the issue of routine primary PCI in NSTEMI is nowadays highly topical, the results we expect in the wake of this pilot study could demonstrate a significant impact on clinical practice. Further research is needed to confirm these results, compare the perforin-mediated activity to other inflammatory mediators in acute coronary events and to examine their impact on the long-term outcome.

Key words: *perforin, cardiovascular disease, atherosclerosis, myocardial infarction, percutaneous coronary intervention*

Introduction

Despite considerable progress in treatment over the past decade, cardiovascular diseases (CVD) are still the leading causes of premature death in Europe[1]. Among all CVD, the coronary artery disease is still associated with significant morbidity and mortality and in Croatia remains the leading cause of death[2]. The well known pathophysiology of myocardial infarction is based on advanced atherosclerosis with superimposed thrombosis, both influenced by various cardiovascular risk factors.

Among them, the inflammatory background of chronic atherosclerosis development and the occurrence of acute myocardial infarction, as its unexpected complication is

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becoming increasingly interesting area of research. Low density lipoproteins accumulated in intima activate the endothelium to express leukocyte adhesion molecules and chemokines (IL-8, macrophage chemoattractant protein 1) that promote their pro-inflammatory Th1 activation and recruitment of immune effectors in the vessel wall[3]. Only lately the important impacts of immune effectors and inflammation on acute coronary atherosclerotic plaque rupture have been investigated. T cells kill vascular smooth muscle cells with the efficacy of lymphokine activated killer[4] using cellular cytotoxic mediators[5] and contribute to plaque destabilisation. The cellular stress proteins including heat shock proteins released from the ruptured plaque and particularly from the infarcted myocardium can induce a further strong proinflammatory response[6,7] by supporting interleukin (IL)-1, IL-12, IL-18, interferon gamma (IFN-g) and tumor necrosis factor alpha (TNF-a) production and secretion in patients with acute coronary syndrome[8,9]. These inflammatory cytokines in the early period after acute myocardial infarction enhance not only local, but also general cell mediated immune response with vascular and myocardial damaging effects in terms of left ventricular performance and patient outcome[10,11]. There are investigations showing that the level of inflammatory reactions gradually regresses spontaneously during the first month after the acute incident and some of the therapeutic procedures, such as physical training, may significantly stimulate their fall[10]. The influence of therapeutic procedures during the early myocardial phase on the subsequent inflammatory response, especially the role of the primary percutaneous coronary intervention (PCI) is one of the most important opened issues.

In addition to further investigation on cytokines, it is also necessary to explore a variety of other potentially harmful mediators that might be involved in the cardiovascular inflammatory reactions. Certainly, one of them is perforin, a quick-action cytotoxic mediator saved together with pro-apoptotic molecules in the cytoplasmic granules of the immune effector-cells (T lymphocytes, NK and NKT cells)[12–14]. After stimulated degranulation, perforin is released into the immunologic synapse and clings to the membrane of target cells creating a cylindrical pore. That way perforin induces target cell necrosis or apoptosis by allowing the access of pro-apoptotic molecules[12,13,15]. Although the precise mechanisms of perforin-mediated cell death are not completely understood, it is considered as the important inflammatory molecule participating in cell mediated killing during the immunological tissue damage[16]. Perforin positive cells were detected in myocardial tissue during Trypanosoma cruzi infection[17] and viral myocarditis[18,19], but the role of this important cytotoxic mediator has been very poorly explored in atherosclerotic cardiovascular diseases[19]. There is insufficient knowledge and understanding about the involvement of perforin in the immune reactions with myocardial infarction during a period of early medical rehabilitation comprising four weeks after the acute myocardial infarction. The aim of this pilot study was to investigate the changes in perforin protein expression in peripheral blood lymphocytes during the early period after acute myocardial infarction, as a function of ongoing inflammation in women with STEMI which underwent PCI and in women with NSTEMI which were conservatively treated.

Materials and Methods

Patients

In this pilot study, we enrolled ten patients in the early period after acute myocardial infarction, during their rehabilitation program at the Clinic for cardiovascular diseases diagnosis, prevention and rehabilitation of the Hospital Thalassotherapia Opatija in Opatija, Croatia. Five women of age 65 (58.25, 73.75) years [median (25^{th}, 75^{th} percentiles)] were with recent ST-segment elevation acute myocardial infarction (STEMI) that has been treated by the primary PCI, while another five women of age 70 years (62.25, 75.75), had the acute myocardial infarction without ST-segment elevation (NSTEMI) and have been conservatively treated. We also included a control group of five age matched healthy women [57 years (56, 70)]. The exclusion criteria were: the presence of uncontrolled hypertension, heart failure, uncontrolled arrhythmias, uncontrolled metabolic disease, significant peripheral vascular disease, active infectious or other inflammatory diseases, childbearing age and chronological age above 80 years.

Patient management

All patients received the routine medical therapy during the study and were included in the education and counselling program in accordance to the European guidelines on the cardiovascular prevention and rehabilitation[1]. There were no differences between groups in the frequency of standard drug therapy use: beta-blocking agents (carvedilol 2 x 6.5 mg), ACE-inhibitors (ramipril 5 mg), statin (atorvastatin 10 mg), antiplatelet agents (acetil salycilyc acid 100 mg and clopidogrel 75 mg in patients with PCI).

Clinical and laboratory parameters

Blood pressure was measured by indirect method. Anthropometric parameters that included the body mass index and the percentage of body fat calculated from skin folds. The standard haematological and biochemical analyzes were performed in every patient using XS-1000i, Sysmex, Kobe, Japan haematology analyser or Dimension Xpand, Siemens Healthcare Diagnostics, Newark, Germany, respectively. Concentration of troponin I value was obtained from patients' medical documentation (discharge summaries) of the Emergency department in Rijeka University Hospital Center.

Immunological methods

Isolation of mononuclear cells from peripheral blood samples on density gradients, the labelling of surface markers and intracellular protein perforin by immunofluore-

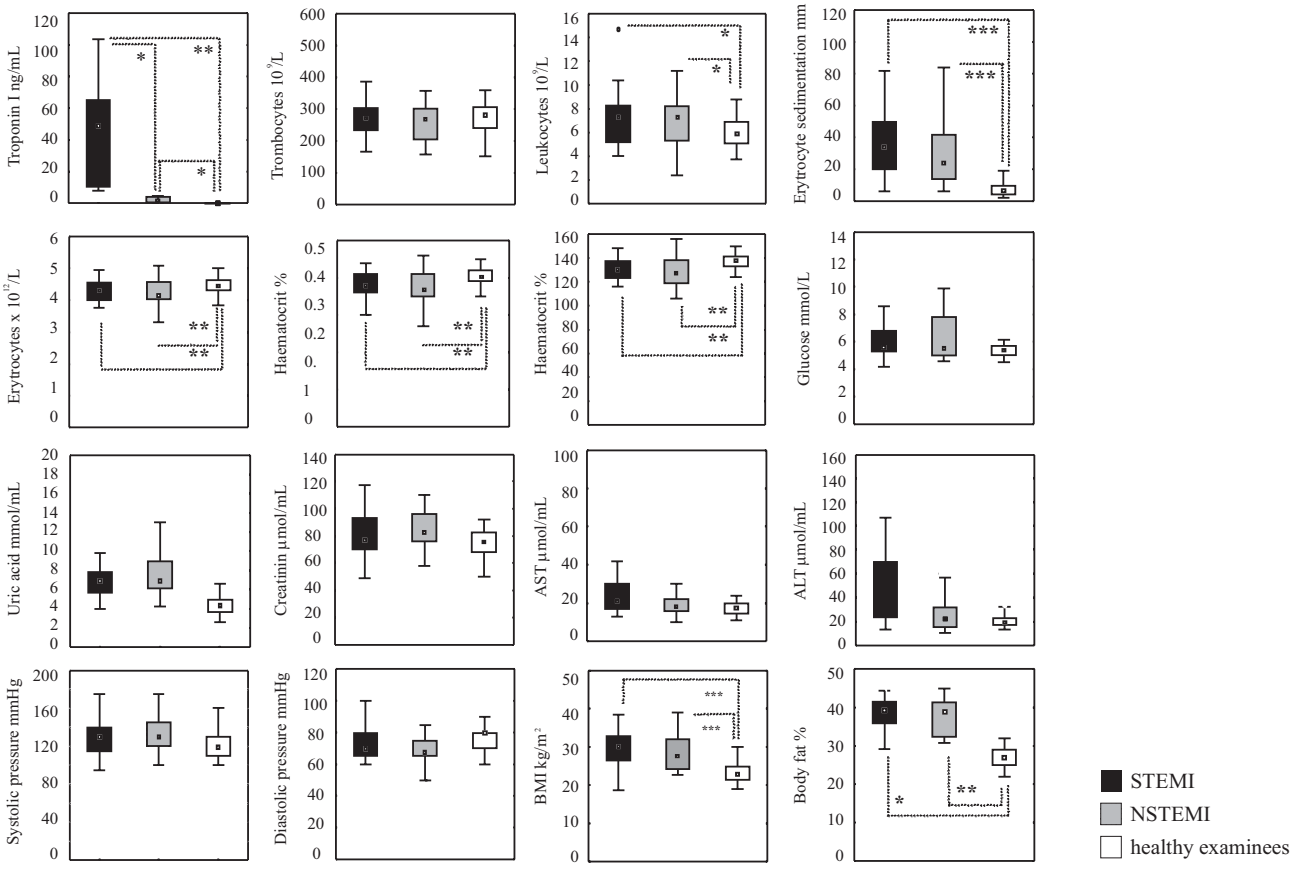

*Fig. 1. Mutual comparisons of the laboratory parameters of women with myocardial infarction with ST segment elevation (STEMI), woman without ST segment elevation (NSTEMI) and healthy examinees. Five experiments were performed. Levels of statistical significance are *p=0.01, **p=0.001, ***p=0.0001.*

scent method and analysis by flow cytometer (FACSCalibur Becton Dickinson) and Cell Quest software (Becton Dickinson) were applied according to the international standardised procedures at the Department of physiology and immunology, School of Medicine, Rijeka, Croatia[20–24].

Statistical analysis

Statistical analysis was performed in Statistica 8.0 (StatSoft, Inc., Tulsa, OK, USA) using non-parametric Kruskal–Wallis. Mann-Whitney U test was used to establish among which groups the difference existed with the level of significance adjusted to the number of mutual comparisons. Data are presented as median values and as 25%–75% (25th percentile – 75th percentile).

Results

Clinical and laboratory characteristic

Clinical and laboratory characteristics were assessed on the day 7 from the onset of myocardial infarction, except the values of troponin I which were measured at the time of clinical presentation (day 1). The values are shown in the Figure 1. Concentration of troponin I in the plasma of STEMI patients was significantly higher then in NSTEMI patients and both groups of patients have higher troponin I concentrations when compared to healthy control. Additionally, accelerated erythrocyte sedimentation rate (ESR), absolute leukocyte number, body mass index (BMI) and percentage of body fat were found in both patients groups compared to healthy population, although the patient groups did not differ between themselves. Absolute erythrocyte number, haemoglobin and haematocrit in women with myocardial infarction were statistically significantly lower than in the healthy women. Systolic and diastolic blood pressure did not basically change between groups investigated.

Perforin expression

In the shown sample the frequency of perforin expressing lymphocytes in healthy women was 23.4% in respect to the isotype control. It did not significantly differ from patients with STEMI on day 7 and 28 (20.4% or 28.57%, respectively), although it was higher then in STEMI patients on day 14 and 21. In patients with NSTEMI, the

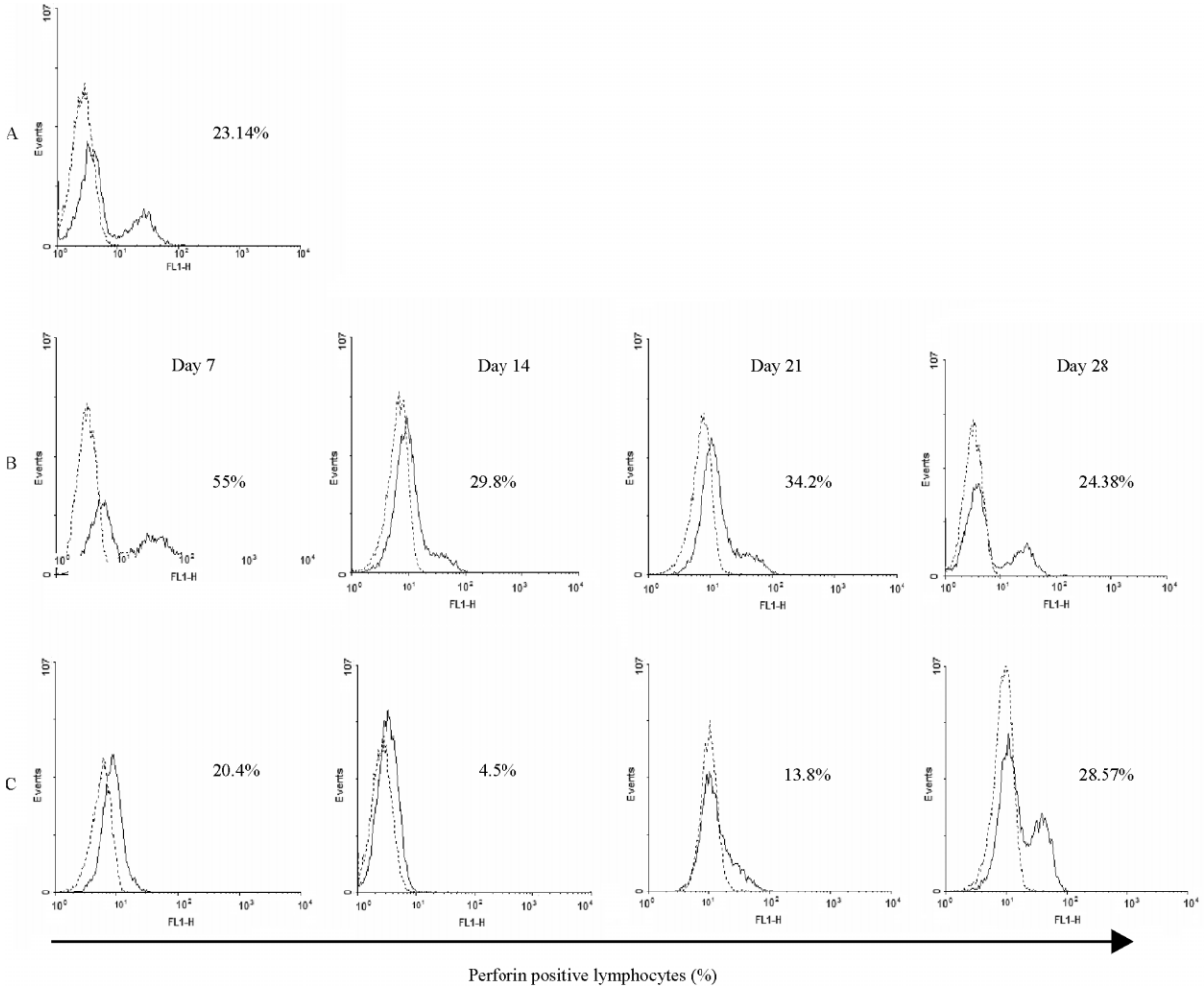

Fig. 2. A sample of flow cytomerty analysis of perforin positive peripheral blood lymphocytes in healthy examinees (A), patients with non ST-elevation (B) and patients with ST-elevation myocardial infarction (C) at indicated time points. Solid histogram curves show indirect labeling with Gd9 anti-perforin mb and goat anti-mouse FITC, whereas dashed histogram curves show labeling with irrelevant isotype matched mouse IgG1.

frequency of perforin expressing lymphocytes was approximately two, six or three times higher than in STEMI patients on day 7, 14 and 21. Perforin expression become basically the same on day 28 in both groups of patients and did not significantly differ from the healthy examinees. Results are shown on the Figure 2.

Discussion and Conclusion

A pleiotropic pro-inflammatory imbalance that occurs in patients with acute myocardial infarction leads to the consolidation of cell mediated immune response[25]. It is still ongoing process in our patients with STEMI and NSTEMI at the beginning of rehabilitation period as it is followed by the accustomed parameters such as absolute number of leukocytes in peripheral blood and accelerated erythrocyte sedimentation rate[26]. The chronic inflammation is confirmed by significantly lower absolute erythrocyte number, haemoglobin concentration and haematocrit that were again found in both groups of patients with myocardial infarction when compared to healthy examinees (Figure 1), although these values do not meet the criteria for anaemia given by World Health Organisation, National kidney foundation or US National Health and Nutrition Examination Survay[27,28]. However, the analysis of perforin expression confirmed (showed) the differences in the pathogenesis of NSTEMI and STEMI[29]. The frequency of perforin expressing lymphocytes, as the more precise inflammatory and activation lymphocyte marker revealed stronger inflammatory reaction in patients with the NSTEMI than in the patients with the STEMI on day 7 after MI in spite of initially significantly lower myocardial tissue necrosis, measured by troponin I concentrations in the plasma. The finding of elevated perforin-positive lymphocytes on the day 7 after myocardial infarction among conservatively treated NSTEMI patients was not beyond our expectation, but the persistence of few times higher percentages of perforin expressing lymphocytes in NSTEMI patients in compari-

son to patients with STEMI till the day 28 certainly was. It is likely that, beside ischemic tissue injury at the culprit vessel and at the site of myocardial infarction, strengthen cellular immune reaction particularly in patients with NSTEMI could additionally damage remote vascular tissue at systemic levels. This hypothesis is in accordance with the previous observation of intra-plaque expansion of auto-antigen specific $CD4^+CD28^-$ T cell clones in patients with ACS[30]. These lymphokine-activated cells functionally resemble NK cells[31] and they are very effective in establishing immunologic synapse with vascular smooth muscle cells and in triggering cell death *in vitro*[32]. These cells produce perforin[30] which is involved in eruption of plaque with superimposed thrombosis and occurrence of MI[32].

Cytotoxicity mediated by perforin is the major effector pathway used by cytotoxic cells[33]. Perforin is potentially dangerous cytotoxic mediator which induces short term necrotic cell death[34,35] by flux and equilibration of ionic gradients in target cells, similarly as final complex of C5-C9 components[34], sometimes for less than 2 hours[36]. Additionally, perforin enables un-scheduled target cell apoptosis by allowing the influx of pro-apoptotic molecules through the perforin pore[37] or perforin acts as a co-factor for the induction of apoptosis in the sublytic concentrations by unknown mechanism[38]. In both cases, the activation of a family of death-inducing proteases called caspases occur[39]. Since perforin could drive target cells apoptosis, it could also activate the anti-inflammatory program mediated by apoptotic cells[40]. However the difference between perforin expression in patients with NSTEMI and STEMI is difficult to explain according to the data available in the scientific publications. Overweight and increased percentage of body fat are generally associated with pro-inflammatory reaction[41], but they are unlikely to be the reasons for increased inflammatory response in patients with NSTEMI since the significant difference in BMI and the percentage of body fat were not observed between patients with STEMI and NSTEMI groups. According to the satisfactory regulation of the blood glucose concentrations and arterial blood pressure it is hard to imagine that they are the reasons for the current worsening of endothelial dysfunction which could activated lymphocytes[30] and increased percentage of perforin expressing cells. According to the experimental model of myocardial infarction, increased early postinfarction perforin expression could be associated with a marked endothelial dysfunction that occurs seven days after coronary artery ligation[42]. It suits well with significant reduction of the frequency of perforin positive lymphocytes in primary PCI treated STEMI patients which is prominent on day 14 after the acute coronary event. It seems that stent re-vascularisation method has the pivotal role in quick quenching the inflammation within the meaning of perforin, beside its clinical benefits for the patients with myocardial infarction[43], since PCI has been the major difference between the examined groups of patients in our pilot study. PCI with stent implantation successfully opens culprit coronary lesion and suspends ischemic myocardial process[44] in STEMI patients with significant myocardial tissue necrosis.

No matter what the cause and mechanism(s) of the decrease of perforin expression were in STEMI patients on the day 14, this finding brings the question of additional benefits that all patients with acute myocardial infarction could have from the early percutaneous interventions. Our preliminary results contribute to the great attention that is nowadays paid to this topic and support the need to introduce routine primary PCI in the treatment of NSTEMI patients[45]. However, toward the better understanding of the role of perforin in myocardial infarction further research is needed to confirm our results, to broad the investigation to the earliest time of its clinical presentation and regulation or even to conduct a study that would prospectively interface the perforin expression and acute coronary event occurrence, the post-myocardial clinical course and the long-term outcome.

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EKSPRESIJA PERFORINA NAKON AKUTNOG INFARKTA MIOKARDA – PILOT-STUDIJA

S A Ž E T A K

Perforin je važan medijator upalnih reakcija, brzodjelujući citotoksični posrednik pohranjen u citoplazmatskim granulama izvršnih stanica imuniteta (T limfocita, NK stanica i NKT stanica) koji posreduje u formiranju smrtonosnog signala spram zaraženih ili drukčije značajno promijenjenih stanica. Perforin-pozitivne stanice otkrivene su u miokardnom tkivu pri kardiovaskularnim bolestima kao što su infekcija Trypanosomom cruzi ili virusni miokarditis, dok je njihova uloga u drugim upalnim bolestima, kao npr. u aterosklerozi i akutnom koronarnom sindromu, gotovo potpuno neistražena. Cilj ovog istraživanja stoga je bio ispitati prisutnost perforina u limfocitima periferne krvi bolesnika tijekom ranog razdoblja nakon akutnog infarkta miokarda. Analizirali smo tri skupine: bolesnice oboljele od akuktnog infarkta miokarda s elevacijom ST-segmenta (STEMI) koje su bile liječene primarnom perkutanom intervencijom (PCI), konzervativno liječene bolesnice s akutnim infarktom miokarda bez elevacije ST-segmenta (NSTEMI) i kontrolnu skupinu dobrovoljki. Skupine STEMI i NSTEMI nisu se razlikovale prema primijenjenoj medikamenoznoj terapiji niti po razinama rutinskih laboratorijskih nalaza, a samo su razine troponina I bile značajno više u STEMI skupini. Zabilježili smo rano smanjenje perforin-pozitivnih limfocita u STEMI-bolesnica koje je bilo u kontrastu s njihovim perzistiranjem unutar NSTEMI skupine. Usprkos većoj nekrozi miokarda u STEMI grupi bolesnica, rezultati ove pilot studije ukazali su na snažnu nishodnu regulaciju peroforina tijekom drugog tjedna nakon infarkta miokarda u ovoj grupi, istakli produljeni upalni odgovor posredovan perforinom u NSTEMI bolesnica, te time skrenuli pažnju na moguću protuupalnu ulogu PCI u akutnom infarktu miokarda. Obzirom da je pitanje primarne PCI u rutinskom zbrinjavanju NSTEMI bolesnika vrlo akutalno, budući rezultati koje na tragu ove pilot studije očekujemo, mogli bi iskazati značajan utjecaj na kliničku praksu. Potrebna su daljnja istraživanja za potvrdu iznesenih rezultata, kao i usporedba perforinom-posredovane upalne aktivnosti s drugim upalnim medijatorima u ranoj fazi nakon akutnog infarkta miokarda, te procjena utjecaja postinfarktne perforinske aktivnosti na dugoročni klinički ishod.