
PhD Thesis

**ANALYSIS OF THE INFLAMMATORY
RESPONSE IN THE DEVELOPMENT AND
EXTENSION OF MYOCARDIAL SCAR TISSUE
DETERMINED BY CARDIAC MRI IN THE
POST-MYOCARDIAL INFARCTION PERIOD**

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SUMMARY

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BACKGROUND

Acute myocardial infarction (AMI) is the most important manifestation of cardiovascular diseases, having a substantial impact on short- and long-term mortality as well as on the quality of life and psychosocial status of patients.

Current research results have demonstrated the important role of inflammation both in the development and vulnerability of atherosclerotic plaques and in the initiation of acute coronary syndromes. Also, systemic, and local inflammation mediates the healing of the post-infarction myocardial injury area that includes ventricular remodelling.

Numerous serum biomarkers are being investigated for an effective assessment of the inflammatory status in patients with cardiovascular diseases, respectively for the determination of the residual risk after an acute cardiovascular event and the prevention of major adverse events.

Cardiac magnetic resonance imaging (MRI) is the gold standard in assessing segmental or global cardiac size, volumes, masses, and function. In addition, this method allows tissue characterization of the myocardium by determining the edematous or necrotic areas after myocardial injury

The aim of this doctoral research was to evaluate the inflammatory response, based on serum biomarkers (hs-CRP, IL-6, selectins, adhesion molecules, matrix metalloproteinases) in the acute period after an acute myocardial infarction revascularized by percutaneous coronary angioplasty and their association with the extension scar tissue determined by cardiac MRI.

MATERIAL AND METHODS

The current research is a prospective, observational one that included a total of 202 patients with a diagnosis of STEMI who underwent myocardial revascularization by pPCI within the first 12 hours of the onset of symptoms, with a follow-up period of 2 years. Subjects were included in 2 substudies.

Substudy 1: included 202 patients with STEMI revascularized by pPCI within the first 12 hours of symptom onset. The aim of this study was to evaluate the impact of the inflammatory response in the acute phase of an AMI on the extent of the myocardial scar determined by cardiac MRI, respectively to determine the predictive ability of serum inflammatory biomarkers and imaging markers on 2-year mortality in patients with STEMI revascularized by pPCI. Demographic, clinical, and angiographic characteristics of the patients were recorded. All patients had serum samples collected on day 1 and day 5 post-infarction for the determination of inflammatory biomarkers. All patients underwent gadolinium-enhanced cardiac MRI (1.5 Tesla) at the one-month follow-up, with image postprocessing using dedicated software, with determination of myocardial volumes and masses, global cardiac function, and quantification of myocardial scar areas.

Substudy 2: included 130 patients with STEMI revascularized by pPCI within the first 12 hours of symptom onset. The purpose of the substudy was to evaluate the relationships between the integrated ST-segment elevation score (ISSTE) - determined before the revascularization procedure and 2 hours after pPCI - serum inflammatory biomarkers in the acute period of MI and myocardial scar extension determined by cardiac MRI.

All procedures in the substudies conform to Good Clinical Practice Guidelines and adhere to the Declaration of Helsinki. Also, the research received the approval of the Ethics Committee of the institution where the study was conducted, and all patients signed the informed consent before the procedures were performed.

RESULTS

Substudy 1 – Analysis of Acute Inflammatory Response in Prediction of MRI-Assessed Myocardial Scar and 2-Year Mortality in Patients with STEMI Revascularized by Primary PCI

202 patients with STEMI treated with primary PCI were included. Based on the mean infarct size (IS) mass values determined at 1-month CMR follow-up, Patients were divided into three groups: tertile I. with IS <14.79 g (n=50), tertile II. with IS 14.79-38.89 g (n=102) and tertile III. with IS>38.89 g (n=50). Serum hs-CRP levels determined on day 1 and 5 post-infarction showed an increasing trend, without significant differences. Serum IL-6 values determined on day 1 were significantly increased in tertile II. III. vs. tertile I (p=0.002). The extent of myocardial scar tissue expressed by IS (mass and volume) was significantly greater in tertile II. and III (10.37±2.90 vs. 25.50±6.54 vs. 54.65±18.01, p<0.0001). The extent of scar tissue with high transmural extension showed significantly increased values in tertile II. and III (p<0.0001). LVEF tended to decrease between tertiles (62.44±9.59 vs. 53.17±10.90 vs. 43.79±10.22, p<0.0001). Significant correlations were identified between IL-6 serum levels and infarct extension (r=0.324, p=0.011), myocardial scar mass with increased transmural extension (r=0.300, p=0.019) and with the percentage of infarcted myocardium (r= 0.303, p=0.018). hs-CRP levels determined on day 5 were identified as predictors for infarct extension at a cut-off value >5.7 mg/L, with AUC 0.635 (p=0.05), sensitivity 53.33% and specificity 1.96%. The extent of the infarct area was identified as a predictor for mortality at 2 years of follow-up with a cut-off value of >28.81 g, with AUC 0.673 (CI 95% 0.60-0.737, p=0.002) with sensitivity 72.41% and specificity 0.58%. Elevated serum levels of IL-6 determined on day 1 post-infarction are significant independent predictors (p=0.04) for increased extension (>38.89 g) of the Hs-CRP infarct area determined on day 5 post-infarction as the strongest independent predictor for mortality at 2-year follow-up (p=0.004).

Substudy 2 - Analysis of relationships of integrated ST-segment elevation score, scar tissue extension and inflammatory response in patients with STEMI revascularized by pPCI

The study included 130 patients with STEMI revascularized by pPCI Based on the means of ISSTE scores (-1 and -2), the included subjects were divided into two groups as follows: ISSTE-1 low/high and ISSTE-2 low/high .. PCI. Day 5 hs-CRP were significantly increased in the increased ISSTE-2 group compared to the low ISSTE-2 group (p=0.031). Similar results were obtained in the case of IL-6. Strong positive significant correlations were observed between ISSTE-2 score and mass of infarcted tissue extension (r= 0.391, P<0.0001) and significant negative correlations with LVEF (r= -0.397, P<0.0001).

CONCLUSIONS

The inflammatory response and its persistence in the acute phase of a STEMI revascularized by pPCI has an impact on the extent of post-infarction scar tissue determined by cardiac MRI at one month follow-up. IL-6 determined on day 1 demonstrated significant associations and correlations with the extension of post-infarction myocardial scar tissue alongside serum values determined on day 5. Day 5 hs-CRP is an independent predictor of all-cause mortality a 2-year follow-up. An increased ISSTE-2 score is illustrative of persistence of ST elevation in the infarcted territory and is associated with increased myocardial scar extension. It is also associated with an increased inflammatory response expressed by elevated serum levels of IL-6 and MMP-9 determined on day 1 and with persistence of inflammation expressed by persistently elevated levels of hs-CRP on day 5 of the acute event.