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Course of inflammatory activation during acute myocardial infarction in patients with preserved left ventricular systolic function

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ABSTRACT

Background. Acute myocardial infarction is associated with a local and systemic inflammatory response which may result in the healing of necrotic myocardium to preserve left ventricular systolic function (LVSF).

Aim. To assess the course of inflammatory activation during hospitalisation and at one month after discharge in patients with preserved global LVSF in six month follow-up after a first acute ST-elevation myocardial infarction (STEMI), treated with primary percutaneous coronary intervention (pPCI).

Material and methods. The study group consisted of 199 patients with STEMI treated with pPCI. The following LVSF echocardiographic parameters were assessed before hospital discharge and at six months after STEMI: left ventricular ejection fraction, wall motion score index and average peak systolic mitral annular velocity. C-reactive protein (CRP) plasma concentrations were measured with an ultra-sensitive latex immunoassay on admission, 24 hours after admission, at discharge and one month after STEMI.

Results. Preserved global LVSF (LVEF $>$ 50%) was present in 24.0% of patients at discharge and in 35.2% of patients at six months after STEMI ($p < 0.001$). Plasma CRP concentration steeply rose in study participants during the first 24 h of hospitalisation ($p < 0.001$) and persisted elevated at discharge. CRP concentrations 24 h after admission, at discharge and at one month after STEMI were lower in patients with preserved global LVSF at six month follow-up compared to patients with LVEF ≤ 50%. Normalisation of CRP concentration after one month occurred exclusively in patients with preserved LVSF at six months. Patients with preserved global LVSF at six months had a lower prevalence of anterior STEMI, diabetes mellitus and symptomatic heart failure at discharge, lower body mass index, more favourable pre-pPCI angiographic flow indices, better final angiographic outcome of pPCI with complete microvascular reperfusion in 57.1% of cases, lower values of myocardial necrosis indices, admission glycaemia, glycated haemoglobin, B-type natriuretic peptide plasma concentration; lower left ventricular volumes and mass and less impaired regional and longitudinal LVSF both at discharge and after six months than patients without preserved global LVSF at six months after STEMI.

Conclusions. Patients with preserved global LVSF at six months after a first STEMI treated with pPCI have a lower intensity of inflammatory response, as assessed by plasma CRP concentration measured during the acute phase, than patients presenting with LVEF ≤ 50% at six month follow-up.

Key words: acute myocardial infarction, left ventricular systolic function, echocardiography, C-reactive protein, inflammation

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Introduction

Acute myocardial infarction is associated with a local and systemic inflammatory response [1–3]. The inflammatory activation may result in the healing of necrotic myocardium to preserve left ventricular (LV) function, but there is experimental evidence that, when exaggerated, it might also promote tissue injury [3]. Decreased myocardial perfusion results in augmented production of non-specific plasma acute-phase proteins, including C-reactive protein (CRP) [4–8]. In experimental models, the concentration of inflammatory mediators increases in the course of acute myocardial necrosis in the initial hours since the onset of symptoms [3]. The tissue inflammatory response is not limited to the area of necrosis, but extends to the intact portions of myocardium [3, 4, 6, 7]. The cytokines released in the process of myocardial damage influence the expansion of necrosis and scar formation by affecting cell growth and migration as well as the repair processes [3]. These mediators also stimulate CRP expression [9, 3, 10]. Literature data also suggests that apart from being an inflammatory marker, CRP should also be regarded as an inflammatory mediator holding pro-thrombotic and pro-apoptotic properties [10–14]. As reported in several studies, elevated CRP levels after acute myocardial infarction are associated with adverse clinical outcomes, including cardiac rupture, LV dysfunction and remodelling, heart failure (HF) and cardiac death, both at hospital discharge and in long-term follow-up [1, 15–24].

Based upon the literature, the prevalence of preserved LV systolic function (LVSF) in post–myocardial infarction patients is estimated to range between 40% and 73%, depending on applied diagnostic criteria (most commonly left ventricular ejection fraction [LVEF]), therapeutic approach and time point of assessment [25–29]. Quick implementation of primary percutaneous coronary intervention (pPCI) with concomitant complete reperfusion in the ischaemic area in the setting of acute ST-elevation myocardial infarction (STEMI) should reduce the area of necrosis and promote the preservation of LVSF [30–33]. Effective reperfusion therapy may modify the course of inflammatory activation during acute myocardial infarction [18, 34–36].

The potential effect of plasma CRP concentration on LV structure and function in patients after acute first STEMI warrants further investigation. While well documented for populations with post-infarct LV systolic dysfunction (LVSD), there is limited data regarding the course of inflammatory activation during acute myocardial infarction in patients with preserved LVSF in long-term follow-up [21, 37–40].

We therefore set out to assess the course of inflammatory activation during hospitalisation and at one month after discharge in patients with preserved global LVSF in six month follow-up after a first STEMI, treated with pPCI.

Material and methods

Study design and patient characteristics

This study was designed as a single-centre prospective observational cohort trial in the setting of first STEMI treated with pPCI, with consecutive patients enrolled in the Department of Cardiology and Internal Medicine of Antoni Jurasz University Hospital in Bydgoszcz between 25 November 2005 and 27 November 2008 [41]. The inclusion criteria were:

- typical stenocardial chest pain of at least 30 minutes' duration;
- onset of symptoms < 12 h before hospital admission;
- electrocardiographic features of acute STEMI (ST-segment elevation ≥0.1 mV or ≥ 0.2 mV in at least two contiguous limbs or precordial leads, respectively).

The exclusion criteria included:

- prior coronary revascularisation;
- cardiogenic shock on admission;
- severe heart failure (New York Heart Association class III or IV);
- bundle branch block;
- permanent atrial fibrillation;
- haemodynamically significant valvular heart disease;
- primary cardiomyopathy;
- severe arterial hypertension;
- creatinine concentration > 176.8 mmol/L;
- presence of features suggestive of an active inflammatory process on admission;
- therapy with steroids, immunosuppressive agents and non-steroidal anti-inflammatory drugs (excluding low doses of aspirin). Diagnosis of diabetes mellitus (DM) was established based on a positive result of oral glucose tolerance test performed on day 3 of hospitalisation or if the patient had been receiving antidiabetic treatment (with oral hypoglycaemic drugs or insulin) [42].

Approval from The Local Bioethics Committee at Collegium Medicum in Bydgoszcz was obtained. All patients gave their written, voluntary, informed consent for participation in the study.

Pharmacotherapy

At first contact with healthcare providers, immediately after establishing the diagnosis of STEMI, all patients were pre-treated with an intravenous bolus of unfractionated heparin (70 IU/kg, up to 5,000 IU) and oral loading doses of clopidogrel (600 mg) and aspirin (300 mg). At the catheterisation laboratory, a second dose of unfractionated heparin was administered intra-arterially in a weight-adjusted manner (up to 100 IU/kg) or under activated clotting time guidance (to the target range of 200-250 seconds) when abcix-

imab was intended. Abciximab was given at the discretion of the invasive cardiologist. Diabetic patients with admission glycaemia ≥ 7.8 mmol/L and those without diabetes with glycaemia of ≥ 10.0 mmol/L on admission were put on short-acting insulin infusion for the first 24 hours of hospitalisation to maintain glucose levels between 7.8 and 10.0 mmol/L [42]. Starting from the second day of hospitalisation, patients with glycaemia levels > 10.0 mmol/L on blood glucose profile received intensive insulin therapy until discharge from hospital, with subsequent therapy with pre-mixed insulin for three months following STEMI [43]. Throughout the study period, clopidogrel and aspirin 75 mg q.d. were continued in all patients. Concomitant medications in the majority of patients included perindopril and long-acting metoprolol in doses adjusted for resting heart rate and blood pressure, and simvastatin 40 mg q.d.. Spironolactone and non-potassium-sparing diuretics were given at the discretion of the cardiologist.

Coronarography and primary percutaneous coronary intervention

Coronarography and pPCI were performed using a standard femoral or radial approach. The use of aspiration thrombectomy during the intervention was left to the operator's discretion. Intracoronary stents were routinely implanted. Coronary artery stenosis was measured with QCA (quantitative coronary angiography). Epicardial coronary flow was assessed according to the TIMI (Thrombolysis in Myocardial Infarction) score and TFC (TIMI frame count), and myocardial perfusion according to the TMPG (TIMI Myocardial Perfusion Grade).

Echocardiography

Transthoracic echocardiographic recordings employing the Doppler technique were acquired at hospital discharge (D) and six months (M6) after STEMI using a Philips SONOS 7500 Ultrasound System, in accordance to the protocol recommended by the American Society of Echocardiography, the European Association of Echocardiography and the Polish Cardiac Society [44–46]. Echocardiographic recordings were assessed offline twice by an experienced echocardiographer blinded to biomarker measurement results. Measurements are reported as an average of three consecutive cardiac cycles. The intra-observer coefficients of variation for LVEF assessed in first 50 patients were below 2.5%.

Diameter, volume and mass indices

The following indices were measured: left atrial end-systolic diameter (LA); LV end-diastolic diameter (LVEDd); LV end-diastolic diameter index (LVEDdI); LV end-diastolic volume (LVEDV); LV end-diastolic volume index (LVEDVI); LV end-systolic diameter (LVESd); LV end-systolic diameter index (LVESd*)*; LV end-systolic volume (LVESV*);* and LV end-systolic volume index (LVESVI*)*. LV mass index (LVMI) was calculated according to the Devereux formula [45]. LV hypertrophy was diagnosed when the value of LVMI was above 117.0 g/m^2 in men and 101.0 g/m^2 in women [45].

Left ventricular systolic function

LVEF, a marker of global LVSF, was calculated using the modified Simpson rule [45]. Wall motion score index (WMSI), reflecting regional LVSF, was derived as a sum of all scores divided by the number of segments visualised, implementing the 16-segment model of LV segmentation and assigning a score from 1 point (normal) to 4 points (dyskinesia), respectively [45]. Measurements of peak mitral annular velocities were obtained for four basal segments of LV (septal, lateral, inferior and anterior) using pulsed tissue Doppler echocardiography with the Doppler gate targeted at the junction of LV walls with the mitral annulus in four- and two-chamber views. Average peak systolic mitral annular velocity (S¢) and average septal and lateral peak systolic mitral annular velocity (S"), the markers of longitudinal LVSF, were obtained [47]. LVSF was classified as follows:

— global — according to the value of LVEF: > 50% — as preserved; ≤ 50% and > 40% — as moderate LVSD; ≤ 40% — as significant LVSD; ≤ 30% — as severe LVSD;
— regional — according to the value of WMSI: < 1.3 — as preserved; ≥ 1.3 and < 1.7 — as moderate LVSD; ≥ 1.7 — as significant LVSD;
— longitudinal — according to the value of S': > 7.5 cm/s — as preserved; ≤ 7.5 cm/s and > 6.0 cm/s — as moderate LVSD; ≤ 6.0 cm/s — as significant LVSD [41, 46, 47].
— As a next step, patients were divided according to the values of LVEF at six months after discharge into two groups: the first group with preserved global LVSF — LVEF > 50% (signified as PLVSF M6+), and the second group without preserved global LVSF — LVEF ≤ 50% (signified as PLVSF M6–).

Left ventricular diastolic function

Diastolic LV function was assessed using pulsed Doppler echocardiography and pulsed tissue Doppler echocardiography by measurements of peak velocity transmitral flow in the early phase (E) and during atrial systole (A) to obtain the E/A ratio, deceleration time of early transmitral flow (DT), isovolumic relaxation time (IVRT*),* reverse pulmonary vein flow (rAv) and the E/E' ratio, where E' is the average peak early diastolic mitral

Table 1. Routine in-hospital laboratory analyses performed during hospitalisation in patients with acute ST-elevation myocardial infarction

Timing	Laboratory analyses
On admission	CK, CK-MB, cTnI, CBC, BUN, creatinine, jonogram, lipid profile, fibrinogen, aPTT, INR, HBs antigen, anti-HCV antibodies, blood group
After 6 h	CK, CK-MB, cTnI, morphology, aPTT
After 12 h	CK, CK-MB, morphology
After 24 h	CK, CK-MB, morphology, BUN, creatinine
At discharge	Morphology

CBC — complete blood count; CK — activity of creatine kinase; CK-MB — activity of izoenzyme MB of creatine kinase

annular velocity [47]. LV diastolic dysfunction was classified as [48]: mild — E/A < 0.8; DT > 200 ms; E/E' ≤ 8; moderate — E/A 0.8–1.5; DT 160–200 ms; E/E' 9–12 or severe — E/A ≥ 2; DT < 160 ms; E/E' ≥ 13.

Blood sampling and laboratory analyses

Routine in-hospital laboratory analyses, performed in each case of acute STEMI in the Department of Cardiology and Internal Medicine of Antoni Jurasz University Hospital in Bydgoszcz, are presented in Table 1. Additional biochemical measurements included troponin I (cTnI) concentration 12 and 24 h after admission and glycated haemoglobin (HbA_{1c}).

Biomarkers

Peripheral venous blood samples were collected using ethylenediaminetetraacetic acid tubes. Until analysed, centrifuged plasma samples were stored at –80°C. CRP plasma concentration was measured with an ultra-sensitive latex immunoassay (CRP Vario test, analyser: ARCHITECT ci 8200, ABBOTT, Wiesbaden, Germany) on admission (CRPa), 24 h after admission (CRP24) and at discharge (CRPd). B-type natriuretic peptide (BNP) plasma concentration was evaluated with a chemiluminescent microparticle immunoassay (analyser: ARCHITECT ci 8200, ABBOTT, Wiesbaden, Germany) on admission (BNPa) and at discharge (BNPd). The limits of detection for CRP and BNP were 0.1 mg/L and 10.0 pg/L, respectively. The intra-assay coefficients of variation were below 2.0% for CRP and below 5.0% for BNP, while the inter-assay coefficients of variation were below 1.0% for CRP and below 5.0% for BNP, respectively.

Statistical analysis

The statistical analysis was carried out using the Statistica 8.0 package. Due to non-normal data distribution, as assessed with the Shapiro-Wilk W-test and the Kolmogorov-Smirnov test, the results are presented as median values and IQ ranges for quantitative variables and as percentages of the population for qualitative parameters. Analysis of the differences between subgroups was performed using a non-parametric test (the Mann-Whitney U-test or the Kruskal-Wallis ANOVA). Wilcoxon's signed rank test was used to evaluate dependent samples. The χ^2 test (with the Yates correction if required) was used for qualitative variables. Two-sided differences were considered significant at $p < 0.05$.

Results

Patients

The study group consisted of 199 patients including 154 men (77.4%) and 45 women (22.6%) with acute STEMI treated with pPCI, who attended the follow-up visit six months after discharge (Table 2**).** Preserved global LVSF (LVEF > 50%) was present in 24.0% of patients at hospital discharge, and in 35.2% of patients at six months after STEMI ($p < 0.001$) (Figure 1).

Clinical, angiographic and biochemical assessment during hospitalisation

Compared to the PLVSF M6– group, patients with preserved global LVSF at six months (PLVSF M6+) had a lower prevalence of anterior STEMI and DM (Table 2**)**. They also had significantly lower values of body mass index (BMI). Symptomatic HF at hospital discharge was a significantly more frequent finding in patients without preserved LVSF at six-month follow-up. Additionally, at hospital discharge only patients in the PLVSF M6– group required treatment with diuretics.

The PLVSF M6+ group presented with noticeably more favourable pre-pPCI angiographic indices of flow in the infarct-related artery (IRA) (less frequent occurrence of culprit lesion in the left descending artery, preserved residual flow in 40.0% of patients) compared to the PLVSF M6– group (Table 3**)**. Also, final angiographic

Table 2. Demographic and clinical characteristics of groups of patients: with (PLVSF M6+ group) and without (PLVSF M6– group) preserved global left ventricular systolic function at six months after discharge

Variable	PLVSF M6+ group (n = 70)	PLVSF M6– group (n = 129)	p PLVSF M6+ vs. PLVSF M6–	
Age (years)	57.0 (50.0–64.0)	56.0 (50.0–64.0)	NS	
Gender (male/female) n (%)	57/13 (81.4/18.6)	97/32(75.2/24.8)	NS	
Anterior wall STEMI n (%)	10 (14.3)	78 (60.5)	< 0.001	
Time from symptom onset to balloon inflation [minutes]	195.0 (145.0–312.0)	203.0 (140.0 285.0)	NS	
BMI [kg/m^2]	25.5 (23.4–27.8)	27.5 (24.6–29.4)	0.005	
Abdominal circumference [cm]	95.0 (88.0–103.0)	100.0 (93.0–107.0)	0.01	NS
Hypertension n (%)	27 (38.6)	55 (42.6)	NS	
Diabetes mellitus n (%)	6 (8.6)	31 (24.0)	0.007	
Angina preceding STEMI n (%)	27 (38.6)	57 (44.2)	NS	
Heart failure (NYHA I/II) prior to STEMI n (%)	1 (1.4)	6 (4.7)	NS	
Current or ex-smoker n (%)	31 (63.3)	103 (66.4)	NS	
Heart failure (NYHA ≥ II) at discharge n (%)	1 (1.4)	19 (14.7)	0.001	
Medical treatment at hospital discharge n (%)				
Acetylsalicylic acid	70 (100.0)	129 (100.0)	NS	
Clopidogrel	70 (100.0)	128 (99.2)	NS	
Simvastatin	69 (98.6)	129 (100.0)	NS	
Perindopril	69 (98.6)	129 (100.0)	NS	
Long-acting metoprolol	70 (100.0)	127 (98.5)	NS	
Spironolactone	0 (0.0)	15 (11.6)	0.003	
Non-potassium-sparing diuretics	0 (0.0)	12 (9.3)	0.008	

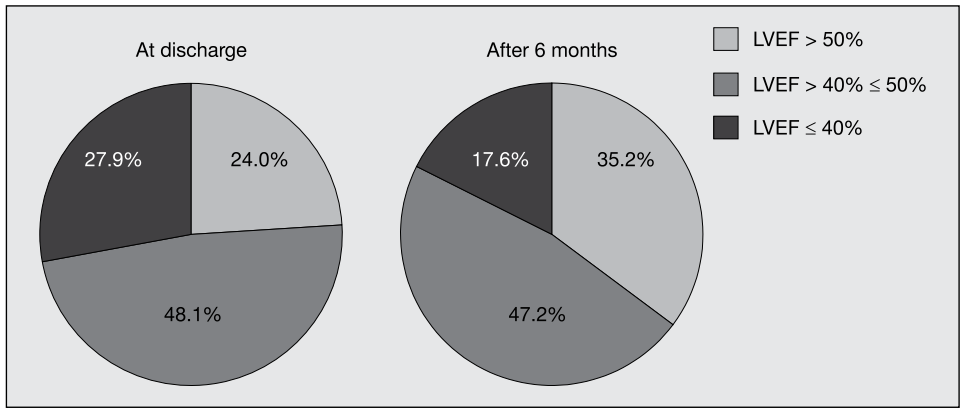

Figure 1. Prevalence of preserved global left ventricular systolic function and left ventricular systolic dysfunction in study population at hospital discharge and six months post-discharge

results of pPCI were better in those with preserved LVSF at six-month follow-up, with complete microvascular reperfusion in more than half of the cases.

Patients with preserved global LVSF presented with significantly lower values of myocardial necrosis indices, admission glycaemia, HbA1c and white blood cell count (WBC) at 24 h after admission (Table 4).

Biomarkers

Admission BNP concentration was higher in patients without preserved LVSF after six months, compared to the PLVSF M6+ group (Table 4). BNP concentration rose during hospitalisation in all patients, predominantly in the PLVSF M6– group, so that the

Table 3. Angiographic characteristics of groups of patients: with (PLVSF M6+ group) and without (PLVSF M6– group) preserved global left ventricular systolic function at six months after discharge

Variable	PLVSF M6+ group (n=70)	PLVSF M6– group (n=129)	p PLVSF M6+ vs. PLVSF M6–
Infarct-related artery: LAD/ non-LAD n (%)	15 (21.4)/55 (78.6)	77 (59.7)/52 (40.3)	< 0.001
Multivessel coronary artery disease n (%)	38 (54.3)	81 (62.8)	NS
Stenosis in QCA (%)			
before pPCI	91.8 ± 10.7	95.3 ± 8.3	0.01
after pPCI	12.8 ± 12.9	11.1 ± 8.2	NS
Flow in TFC [frames/s]			
before pPCI	67.6 ± 35.3	79.5 ± 31.7	0.016
after pPCI	22.2 ± 15.4	27.8 ± 19.1	0.036
TIMI flow n (%)			
TIMI 0-1 before pPCI	35 (50.0)	87 (67.4)	0.03
TIMI 3 before pPCI	28 (40.0)	27 (20.9)	0.03
TIMI 3 after pPCI	67 (95.7)	118 (91.5)	NS
TMPG 3 after pPCI n (%)	40 (57.1)	52 (40.3)	0.023
Patients with implanted stents n (%)	68 (97.1)	129 (100.0)	NS
Patients with implanted DES n (%)	1 (1.4)	2 (1.6)	NS
Abciximab use n (%)	12 (17.1)	38 (29.4)	0.05

LAD — left anterior descending artery; DES — drug-eluting stent

Table 4. Biochemical characteristics of groups of patients: with (PLVSF M6+ group) and without (PLVSF M6– group) preserved global left ventricular systolic function at six months after discharge

Variable	PLVSF M6+ group (n = 70)	PLVSF M6– group (n = 129)	p PLVSF M6+ vs. PLVSF M6–
CK-MBa [U/l]	24.0 (18.0–34.0)	28.0 (18.0–51.0)	0.044
CK-MB24 [U/l]	84.0 (44.5–123.0)	110.0 (64.0–164.0)	0.006
$CK\text{-}MB_{max}$ [U/l]	86.0 (47.5–127.5)	119.0 (68.0–178.0)	0.002
cTnIa [ng/mL]	0.26 (0.05–0.95)	0.28 (0.08–1.18)	NS
$cTnI_{max}$ [ng/mL]	24.2 (7.9– > 50.0)	> 50.0 (16.8–> 50.0)	0.001
Creatinine [μmol/L]*	79.6 (70.7–93.7)	84.9 (76.0–97.2)	NS
Haemoglobin [mmol/L]*	14.5 (13.7–15.3)	14.7 (13.6–15.5)	NS
WBCa	10.6 (9.0–12.8)	11.6 (9.1–13.5)	NS
WBC24	9.8 (8.2–11.2)	10.4 (8.8–12.3)	0.002
Admission glycaemia [mmol/l]	7.1 (6.4–8.1)	7.9 (6.9–9.7)	0.008
HbA1c [%]	5.9 (5.5–6.4)	6.2 (5.7–6.8)	0.035
TC [mmol/L]*	5.7 (5.0–6.2)	5.8 (5.1–6.6)	NS
LDL-C [mmol/l]*	3.8 (3.2–4.3)	3.7 (3.3–4.5)	NS
HDL-C [mmol/l]*	1.3 (1.2–1.5)	1.3 (1.2–1.5)	NS
TG [mmol/l]*	0.9 (0.7–1.4)	1.1 (0.7–1.7)	NS
BNPa [pg/mL]	41.7 (20.0–75.0)	56.9 (30.2–129.2)	0.028
BNPd [pg/mL]	86.5 (56.0–156.2)	152.6 (83.8–299.9)	< 0.001
BNPa-d [pg/mL]	42.2 (14.9–81.3)	74.7 (7.5–199.8)	0.004
CRPa [mg/L]	1.93 (0.84–3.3)	1.74 (1.15–3.28)	NS
CRP24 [mg/L]	7.55 (4.75–11.7)	13.04 (6.21–23.27)	0.002
CRPd [mg/L]	9.07 (3.89–14.4)	10.44 (5.84–20.68)	0.006
CRP M1 [mg/L]	1.38 (0.77–3.44)	1.77 (0.97–3.07)	0.045

*on admission

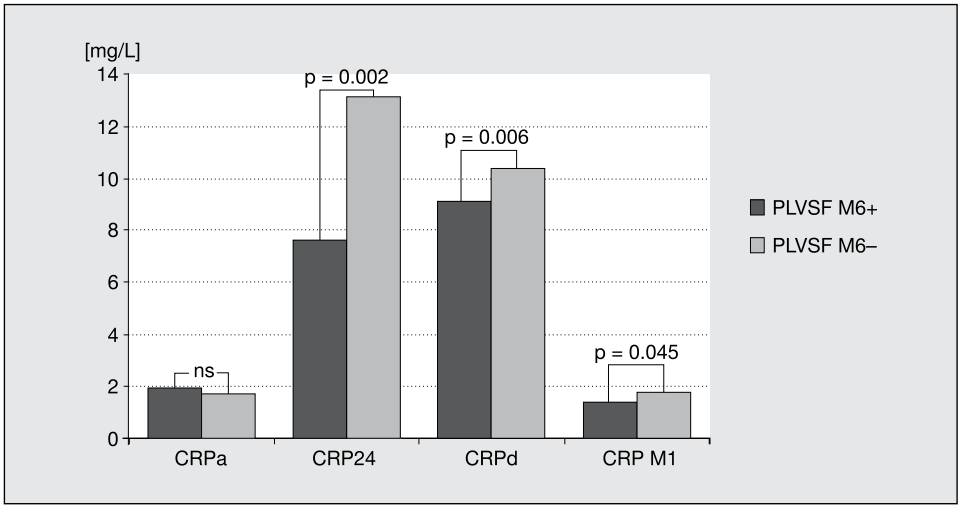

Figure 2. C-reactive protein plasma concentrations on admission, 24 hours after admission, at hospital discharge, and at one month after STEMI in patients with and without preserved global left ventricular systolic function after six months

latter group presented with remarkably higher BNP levels at discharge.

At baseline, there were no significant differences in CRP concentration between patients with and without preserved global LVSF at six months (Table 4, Figure 2). Plasma CRP concentration steeply rose during the initial 24 h of hospitalisation ($p < 0.001$), mainly in the PLVSF M6– group, and persisted elevated at discharge in both groups (Figure 2). CRP concentrations 24 h after admission, at discharge and at one month after STEMI were significantly lower in patients with preserved global LVSF at six month follow-up (Table 4). Additionally, normalisation of CRP concentration after one month occurred exclusively in patients with preserved LVSF at six months.

Echocardiographic assessment at discharge and after six months

At baseline, patients with preserved global LVSF after six months presented with moderate global and regional LVSD and preserved longitudinal LVSF (Table 5). At hospital discharge, the PLVSF M6– group had significantly higher values of LV volumes and mass than patients with LVEF > 50% at six months. Significantly higher WMSI and markedly lower S' values were observed in the former group, indicating more impaired regional and longitudinal LVSF. At baseli ne, there was significant regional and moderate global and longitudinal LVSD in the PLVSF M6– group.

At six month follow–up, we observed an increase in left heart chamber sizes, LVMI and LVEF with a concomitant decrease in WMSI and S' in both groups. Finally, after six months the PLVSF M6– group had significantly larger diameters of LA and LV, higher systolic and diastolic LV volumes, and greater LVM than patients with preserved global LVSF. The regional and longitudinal LVSF were moderately impaired in both groups, though the decline was greater in the PLVSF M6– group than in their counterparts with preserved global LVSF after six months. Also, the echocardiographic indices of LV diastolic function were more abnormal in the PLVSF M6– group, though moderate LV diastolic dysfunction was noted in both groups.

Discussion

The present study shows a lower intensity of inflammatory response, as assessed by plasma CRP concentration measured during the acute phase of a first STEMI treated with pPCI, in patients with preserved global LVSF at six months after hospital discharge, compared to patients with LVEF ≤ 50% at six month follow-up. The results of our study describe the course of inflammatory activation during the acute STEMI in patients with preserved LVSF in long-term observation. According to our findings, this group of patients is subject to a severe early inflammatory reaction as indicated by the dynamic changes in CRP concentration, with its steep rise during first 24 hours of hospitalisation, persistent elevation until hospital discharge and subsequent normalisation within one month after STEMI. Patients with LVEF > 50% at six-month follow-up however presented with a less abrupt, significantly lower and shorter-lasting increase in CRP concentration. Additionally, CRP concentration normalised after one month only in these patients. Thus, CRP concentration at each assessed time point was lower in this group of patients compared to those without preserved LVSF at six month follow-up.

Table 5. Echocardiographic characteristics of groups of patients: with (PLVSF M6+ group) and without (PLVSF M6– group) preserved global left ventricular systolic function at six months after discharge. Echocardiographic indices are derived from 2D, Doppler echocardiography and tissue Doppler echocardiography at hospital discharge and at six months after discharge, respectively

Variable	PLVSF M6+ group (n = 70) Hospital discharge	PLVSF M6+ group (n = 70) After six months	PLVSF M6– group (n = 129) Hospital discharge	PLVSF M6– group (n = 129) After six months	p PLVSF M6+ vs. PLVSF M– Hospital discharge	p PLVSF M6+ vs. PLVSF M6– After six months
LA [mm]	38.5 (36.0–42.0)	39.0 (37.0–43.0)	40.0 (37.0–42.0)	41.0 (38.0–45.0)	NS	0.04
LVEDd [mm]	48.0 (43.0–51.0)	48.0 (45.0–51.0)	49.0 (46.0–54.0)	51.0 (46.0–56.0)	0.01	< 0.001
LVEDdI [mm/m^2]	25.4 (23.0–26.9)	25.9 (24.7–27.3)	25.5 (23.2–27.8)	26.5 (24.1–28.9)	NS	0.006
LVESd [mm]	32.0 (29.0–35.0)	33.0 (30.0–35.0)	34.0 (31.0–38.0)	35.0 (32.0–39.0)	< 0.001	< 0.001
LVESdI [mm/m^2]	17.5 (15.1–18.5)	17.8 (16.0–18.6)	17.4 (16.1–19.9)	18.2 (16.4–20.2)	0.007	< 0.001
LVMI [g/m^2]	105.5 (94.8–121.1)	112.7 (99.0–123.1)	120.7 (99.9–137.0)	123.1 (103.7–140.4)	< 0.001	< 0.001
LVEDV [ml]	90.0 (80.0–104.0)	100.0 (88.0–117.0)	103.0 (85.0–122.0)	120.0 (94.0–146.0)	< 0.001	< 0.001
LVEDVI [ml/m^2]	47.5 (42.8–54.0)	55.7 (48.1–65.1)	54.0 (45.4–62.6)	61.8 (50.3–76.9)	0.002	< 0.001
LVESV [ml]	45.0 (40.0–52.0)	47.0 (40.0–55.0)	59.0 (48.0–72.0)	67.5 (51.7–84.0)	< 0.001	< 0.001
LVESVI [ml/m^2]	23.8 (21.7–27.7)	26.4 (23.0–30.0)	30.2 (25.4–37.7)	35.5 (27.7–43.8)	< 0.001	< 0.001
LVEF [%]	50.0 (47.0–51.8)	53.0 (51.7–55.0)	42.0 (38.0–45.0)	43.2 (40,0–45.5)	< 0.001	< 0.001
WMSI [pkt]	1.38 (1.31–1.44)	1.31 (1.25–1.38)	1.69 (1.44–1.81)	1.56 (1.44–1.75)	< 0.001	< 0.001
DT [ms]	165.0 (150.0–190.0)	180.0 (155.0–200.0)	155.0 (145.0–185.0)	165.0 (155.0–195.0)	NS	0.04
IVRT [ms]	95.0 (85.0–110.0)	105.0 (100.0–115.0)	95.0 (90.0–110.0)	105.0 (90.0–115.0)	NS	NS
E/A[–]	1.08 (0.79–1.5)	0.97 (0.81–1.24)	0.86 (0.72–1.23)	0.93 (0.73–1.43)	NS	NS
E/E'[–]	9.5 (8.1–11.2)	8.5 (7.6–10.5)	10.9 (8.6–13.2)	10.0 (8.3–12.8)	0.034	0.002
rAv [cm/s]	29.0 (26.0–32.0)	28.0 (26.0–32.0)	29.0 (27.0–33.0)	29.0 (27.0–34.0)	NS	0.032
S' [cm/s]	7.7 (6.6–8.8)	7.3 (6.4–8.0)	6.9 (6.0–7.8)	6.8 (5.8–8.2)	< 0.001	0.033
S" [cm/s]	7.6 (6.8–8.9)	7.4 (6.5–8.4)	6.7 (6.0–7.9)	7.0 (5.7–8.1)	< 0.001	< 0.001

Our study confirms previous evidence of the presence of a significant increase in CRP concentration in the course of myocardial infarction [3, 5, 20]. As reported in several studies, the peak concentration of CRP is observed about two days from the onset of STEMI, then it decreases over the first week, and decreases further within one month, to return to normal values after several weeks (most often 4–6) after STEMI [1–3, 13, 18, 19, 49–53]. Mather et al. found the decrease in CRP concentration in the period between one and three months insignificant [53].

Myocardial necrosis due to abrupt closure of coronary artery in case of acute myocardial infarction leads to a systemic and regional humoral and cellular inflammatory response [9, 54, 55]. In the early phase of myocardial infarction, the inflammatory response is particularly strong in the infarct region and in the border zone, aiming to promote the local myocardial healing process and scar formation [9, 54, 55]. In the beginning of acute STEMI, cytokines play an important cyto-protective role, mainly by reducing cell apoptosis [3, 56]. The process is facilitated by a dynamic balance between interactions involving leukocytes, platelets and endothelium cells on the one hand, and the excretion of cytokines modulating the process on the other hand [3]. However, increased and prolonged CRP expression promotes further enhancement of the necrosis area [9]. CRP binds to phosphocholine groups of necrotic myocardial cell membranes, facilitating complementary activation and thus promoting further inflammatory response, injury of myocardial cells and expansion of necrosis [3, 10–13]. Literature data suggests that CRP should be considered an inflammatory mediator holding pro-thrombotic and pro-apoptotic properties associated with increased apoptotic rates, macrophage infiltration, monocyte chemotactic protein expression-1 and matrix metalloproteinase-9 activity in the border zone [10, 12, 15, 24]. Additionally, CRP reduces the bioavailability of nitric oxide, which in turn suppresses angiogenesis and also inhibits endothelial progenitor cell differentiation, cellular function and survival, leading to further expansion of tissue injury due to ischaemia and reperfusion [10, 12, 15, 24].

As reported in several studies, the intensity and sustained increase in plasma CRP concentration in the course of myocardial infarction may be associated with a greater extent of myocardial damage reflected by the values of cardiac necrosis markers [20, 35, 50, 54, 57]. It is known that a strong correlation exists between CRP levels, infarct size, and biochemical markers of myocardial necrosis [20, 35, 50, 54, 57]. The findings by Ørn provide a potential pathophysiological explanation for the association between CRP levels and LV remodelling, by linking peak CRP levels with infarct size after two months [20]. Aggepoulos et al. observed significantly higher baseline activity of troponin in patients admitted to hospital for acute coronary syndrome with higher levels of CRP measured within the initial 12 hours of hospitalisation [21]. Also in our study, which included patients with a first STEMI undergoing pPCI, the PLVSF M6– group exhibiting a more pronounced inflammatory response, presented with larger infarctions as assessed by enzymatic assays, mainly of anterior location [17, 58–60]. This is consistent with an observation by Damman et al., who found a higher risk of depressed LVEF at six months after discharge in patients with acute STEMI, specifically of anterior location [60].

In the present study, patients from the PLVSF M6+ group presented with a less severe inflammatory response in the course of myocardial infarction and with a higher incidence of IRA and microcirculation reperfusion. As demonstrated by Ørn et al., individuals with persistent microcirculation obstruction in the course of STEMI present with increased CRP levels [20]. Elevated CRP levels during hospitalisation for STEMI have also been proven to correlate with persistent microcirculation dysfunction and significantly poorer myocardial perfusion in acute anterior wall STEMI patients treated with pPCI [61, 62]. Also, Mayr et al. found a significant correlation between coronary microvascular obstruction, as quantified by cardiac magnetic resonance imaging within eight days after successful interventional reperfused first acute STEMI, and CRP concentration measured during the initial four days of hospitalisation [63].

The lesser severity of inflammatory reaction in the acute phase of STEMI, observed in the present study among patients with preserved LVSF in long-term follow-up, might be attributed to a significantly lower prevalence rate of DM in the study population. The presence of DM in patients with acute STEMI is associated with aggravation of the systemic inflammatory reaction and elevation of CRP concentration [64]. According to the Munich Myocardial Infarction Registry, CRP concentration in diabetic patients is significantly higher from the very beginning of hospitalisation than in those without diabetes [65]. Also, Piestrzeniewicz et al. reported a higher prevalence of DM in the upper quartiles of admission CRP concentration in a study including 70 men admitted to hospital for acute STEMI [66]. These findings might be indicative of occurrence of inflammatory activation in patients with concurrent STEMI and DM, taking place prior to hospital admission. In a study by Suleiman et al., when comparing the first against the fourth quartile of CRP level at hospital discharge, the percentage of patients with DM was significantly higher in the group with CRP levels in the fourth quartile [40]. As demonstrated above, in the population of STEMI patients observed in the present study, CRP concentration in diabetic patients, in contrast to those without diabetes, was continuously increasing from the very beginning and then throughout the entire hospitalisation period, reaching peak values at discharge, without subsequent normalisation within one month after STEMI [67]. These findings may support the existence of enhanced inflammatory activation in STEMI patients with concurrent DM, as indicated by other literature data [68].

Compared to the PLVSF M6– group, the course of the inflammatory reaction in STEMI patients with preserved LVSF in long-term follow-up may be modified by lower levels of in-hospital glycaemic control parameters such as admission glycaemia and HbA1c. Admission hyperglycaemia in STEMI patients has been shown to be a predictor of worse short- and long-term outcomes as well as with elevated levels of inflammatory markers [69–71]. As reported by Piestrzeniewicz, there was a significant correlation between elevated admission glycaemia (> 144 mg/dL) and increased CRP concentration on admission in a group of 70 men with acute STEMI [66]. The correlation between CRP concentration and the average 24-hour glycaemic profile measured on the second day of hospitalisation, reported by our team in a previous study, may indicate an association between elevated in-hospital glycaemia levels and the intensity of the inflammatory reaction in this group of patients [67].

Furthermore, in our study overweight and obese patients were more likely to present with LVEF $\leq$ 50% at six months. According to literature data, high BMI, by its frequent co-existence with the proinflammatory state, may indicate the presence of inflammatory activation before STEMI, in this group of patients [72–74].

Compared to the PLVSF M6– group, patients with preserved global LVSF present at six month follow-up showed lower BNP levels during hospitalisation. Cardiac natriuretic peptides reflect the ventricular function impairment and haemodynamic decompensation in the course of myocardial infarction, associated with the size of necrotic area and intensity of inflammatory response [17]. According to the findings by Haeck et al., there is a strong relationship between BNP and CRP in the early phase of acute STEMI [75]. Similarly, in the APEX-AMI study (An Assessment of Pexelizumab in Acute Myocardial Infarction Substudy), including

5,745 patients with acute STEMI treated with pPCI, van Diepen et al. found significant correlations between interleukin-6 and CRP and BNP concentration, also in patients without symptoms of HF [76]. As suggested by these observations, the inflammatory process could possibly affect the expression of natriuretic peptides through pathways distinct from sole enhancement of LV wall tension.

Significantly lower WBC24 values seen in patients with preserved LVSF at six months after STEMI prove a lower intensity of the in-hospital inflammatory response in patients with acute coronary syndrome in this group of patients. Literature data suggests a significant correlation between WBC count, levels of myocardial necrosis markers, and CRP plasma concentration. Thus, it seems justified to regard WBC count as a prognostic biomarker for predicting the size of necrotic area and the intensity of the inflammatory reaction in STEMI patients [21, 77]. Chia et al. defined the increase in WBC count and neutrophilia in PCI-treated STEMI patients as an independent predictor of MACE in long-term follow-up by proving their significant association with the infarction size and LVEF value [78]. Moreover, it has been demonstrated in experimental models that neutropenia is associated with a smaller infarction size [79].

In our study including patients with a first STEMI treated invasively, the prevalence of LVEF > 50% at discharge was estimated to be 24.0%. The more frequent (52% and 60%) occurrence of preserved LVSF before discharge reported in French registries USIC 2000 (Unite de Soin's Intensifs Coronaires) and LVEF ≥ 50% in the MAGIC Trial (Magnesium in Coronaries Trial) may result from the smaller percentage of STEMI patients in these studies (merely 89 and 59%), compared to ours [26, 29]. The lower prevalence of preserved LVSF in pre-discharge assessment reported in other registries and studies may also be associated with the timing of the initial echocardiographic assessment, commonly performed in the early phase of acute STEMI (i.e. usually on the third day) [26, 29]. We observed restoration of LVEF with more frequent occurrence of LVEF > 50% after six months (35.4%) compared to the baseline values. According to data from literature, the prevalence of preserved LVSF in STEMI population is more frequent than in our study, being estimated at 70–78% after 4-6 months from discharge. Those discrepancies however may be due to more liberal criteria for preserved LVSF (LVEF > 40–45%) employed in other studies [19, 80, 81].

Having applied similar criteria in our study, LVEF > 40% was found in 80.4% of patients at six months after hospital discharge. There is only sparse long-term follow-up data available on LVSF in post-STEMI patients treated with pPCI [80, 82–87]. Several researchers have reported significant improvements in LVSF at 3–6 months after STEMI. While van Melle et al. defined the LVSF improvement as an increase in LVEF by 6% or more, Parodi et al. used a threshold of ≥ 10% [80, 82]. With the latter value applied, LVSF improvement six months after STEMI was seen in 58% of patients [83]. Antoni et al. found improvement in LVSF, defined as a ≥ 10% decrease in global longitudinal peak systolic strain assessed at one year after STEMI, in 72% of evaluated patients [85].

The improvement in LVSF in long-term follow-up after STEMI depends on multiple factors, including myocardial stunning reversal and the size of reperfused myocardium, particularly in patients with anterior wall myocardial infarction [58, 85–90]. Concerning preservation of LV function after STEMI treated with pPCI, it is crucial to re-establish normal blood flow in the IRA and achieve complete reperfusion in the coronary microcirculation [91]. Early achievement of optimal angiographic outcome significantly reduces the area of myocardial necrosis, thus allowing the preservation of LVSF after STEMI [32, 33, 92]. An association between impaired coronary microcirculation perfusion and decreased EF or lack of LV systolic function recovery at three months after pPCI-treated STEMI has already been reported in previous publications [93, 94].

In the present study, patients with preserved LVSF in long-term follow-up after STEMI showed a higher incidence of complete myocardial reperfusion, as assessed by TMPG, than their counterparts from the PLVSF M6– group (57% vs. 40%). As suggested by literature data, favourable angiographic characteristics prior to PCI may also be beneficial in terms of LVSF preservation in long-term follow-up after STEMI [58, 95]. Indeed, as demonstrated in the present study, compared to their counterparts from the PLVSF M6– group, patients presenting with preserved global LVSF at six months following hospital discharge were found to have a lower rate of severe IRA obstruction and more frequent preservation of residual blood flow in the IRA before pPCI. Even modest residual flow in the IRA preceding pPCI is beneficial in terms of LV function recovery, possibly due to shortening the duration of ischaemia with resultant reduction in infarction size, but also due to preventing the 'no reflow' phenomenon [86, 95].

According to Parodi et al., the predictors of LVSF improvement in long-term follow-up in patients treated with pPCI for STEMI include: small enzymatic infarct size, short duration of time from symptom onset to reperfusion, mild impairment of regional LVSF in echocardiographic assessment within 24 hours of hospital admission, and female gender [82]. Also the APEX-TIMI trial identified infarction size as an independent predictor of LVEF at three months after STEMI treated with pPCI [94]. In a study by Hassan et al. including 168 patients treated with pPCI for acute STEMI, peak

troponin level was the most important independent predictor of LVEF at three months after STEMI [96]. In the present study, patients with preserved LVSF in long-term follow-up after STEMI had significantly lower levels of myocardial necrosis markers than individuals from the PLVSF M6– group, both on admission and after the initial 24 hours of hospitalisation. Furthermore, the former group, in contrast to the latter, showed no significant regional LVSD at hospital discharge. Also, in patients with LVEF > 50% at discharge, the anterior wall location of myocardial infarction, usually associated with more extensive myocardial necrosis, was significantly less common.

We also found lower in-hospital levels of glycaemic control indicators and lower prevalence of DM among patients with preserved global LVSF compared to the PLVSF M6– group. Literature data supports the existence of higher admission glycaemia levels in acute STEMI patients with a larger infarction size and concomitant LVSD [70, 97]. Additionally, previously we have reported associations between LVEF at 12 months after STEMI and admission levels of glycaemia and HbA1c [87], thus supporting the observation of other researchers, claiming that the co-existence of DM may impose a significant impact on LVSF in STEMI patients in long-term follow-up [98–99].

Limitations of this study

The present study has several limitations. Due to early achievement of reperfusion, the patients had relatively well-preserved LV function. We did not account in our calculations for diurnal and seasonal variations in CRP concentration. Also, lack of concomitant assessment of cytokines and growth factors are important limitations. Further efforts are warranted to confirm the clinical significance of our findings and to fully explain the mechanisms through which the inflammatory process is associated with LVSF.

Conclusions

Patients with preserved global LVSF at six months after a first STEMI treated with pPCI have a lower intensity of inflammatory response, as assessed by plasma CRP concentration measured during the acute phase, compared to patients presenting with LVEF ≤ 50% at six month follow-up. In patients with preserved global LVSF in long-term observation, CRP concentration steeply rises during the first 24 hours of hospitalisation, persists elevated until hospital discharge, and normalises within one month after STEMI. The lower intensity of inflammatory activation in the course of STEMI in patients with preserved global LVSF in long-term follow-up may be associated with the following factors: smaller infarction size; more favourable pre-pPCI angiographic characteristics; better final angiographic outcome of pPCI with a higher rate of normal blood flow restoration in IRA and coronary microvascular reperfusion; milder post-infarct LV haemodynamic decompensation; lower prevalence of DM; and lower values of admission glycaemic indices and BMI.

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Conflict of interest

We have no conflict of interest concerning this study.

References

1. Anzai T, Yoshikawa T, Shiraki H et al. C-reactive protein as a predictor of infarct expansion and cardiac rupture after a first Q-wave acute myocardial infarction. Circulation 1997; 96: 778–784.
2. James S, Oldgren J, Lindback J et al. An acute inflammatory reaction induced by myocardial damage is superimposed on a chronic inflammation in unstable coronary artery disease. Am Heart J 2005; 149: 619–626.
3. Nian M, Lee P, Khaper N et al. Inflammatory cytokines and postmyocardial infarction remodeling. Circ Res 2004; 94: 1543–1553.
4. Deten A, Volz H, Briest W et al. Cardiac cytokine expression is upregulated in the acute phase after myocardial infarction. Experimental studies in rats. Cardiovasc Res 2002;55: 329–340.
5. Frangogiannis N, Smith C, Entman M et al. The inflammatory response in myocardial infarction. Cardiovasc Res 2002; 53: 31–47.
6. Gwechenberger M, Mendoza L, Yourker K et al. Cardiac myocytes produce interleukin-6 in culture and in viable border zone of reperfused infarctions. Circulation 1999; 99: 546–551.
7. Irwin M, Mak S, Mann D et al. Tissue expression and immunolocalisation of tumor necrosis factor-alpha in postinfarction dysfunctional myocardium. Circulation 1999; 99: 1492–1498.
8. Valgimigli M, Ceconi C, Malagutti P et al. Tumor necrosis factor alpha receptor 1 is a major predictor of mortality and new–onset heart failure in patients with acute myocardial infarction: the Cytokine-Activation and Long-Term Prognosis in Myocardial Infarction (C-ALPHA) study. Circulation 2005; 111: 863–870.
9. Bonvini R, Hendiri T, Camenzind E. Inflammatory response post–myocardial infarction and reperfusion: a new therapeutic target? Eur Heart J 2005 Suppl; 7: I27–I36.
10. Griselli M, Herbert J, Hutchinson W. i wsp. C–reactive protein and complement are important mediators of tissue damage in acute myocardial infarction. J Exp Med 1999; 190: 1733–1740.
11. Kitsis R, Jialal I. Limiting myocardial damage during acute myocardial infarction by inhibiting C–reactive protein. N Engl J Med 2006; 355: 513–515.
12. Lagrand W, Niessen H, Wolbink G et al. C–reactive protein colocalizes with complement in human hearts during acute myocardial infarction. Circulation 1997; 95: 97–103.

13. Pepys M, Hirschfield G. C-reactive protein: a critical update. J Clin Investigation 2003; 111: 1805–1812.
14. Pepys M, Hirschfield G, Tennent G et al. Targeting C-reactive protein for the treatment of cardiovascular disease. Nature 2006; 440: 1217–1221.
15. Anzai T, Yoshikawa T, Kaneko H et al. Association between serum C-reactive protein elevation and left ventricular thrombus formation after first anterior myocardial infarction. Chest 2004; 125: 384–389.
16. Shah S, Marcus G, Gerber J et al. High-sensitivity C-reactive protein and parameters of left ventricular dysfunction. J Card Fail 2006; 12: 61–65.
17. Urbano-Moral J, Lopez-Haldon J, Fernandez M et al. Prognostic value of different serum biomarkers for left ventricular remodelling after ST--elevation myocardial infarction treated with primary percutaneous coronary intervention. Heart 2012; 98: 1153–1159.
18. Dedobbeleer C, Melot C, Renard M et al. C-reactive protein increase in acute myocardial infarction. Acta Cardiol 2004; 59: 291–296.
19. Karpiński Ł, Płaksej R, Kosmala W et al. Serum levels of interleukin-6, interleukin-10 and C-reactive protein in relation to left ventricular function in patients with myocardial infarction treated with primary angioplasty. Kardiol Pol 2008; 66: 1279–1285.
20. Ørn S, Manhenke C, Ueland T et al. C-reactive protein, infarct size, microvascular obstruction, and left–ventricular remodelling following acute myocardial infarction. Eur Heart J 2009; 30: 1180–1186.
21. Aggelopoulos P, Chrysohoou C, Pitsavos C et al. Comparative value of simple inflammatory markers in the prediction of left ventricular systolic dysfunction in postacute coronary syndrome patients. Mediat Inflamm 2009; 20: 35–42.
22. Świątkiewicz I, Koziński M, Magielski P et al. Usefulness of C-reactive protein as a marker of early post-infarct left ventricular systolic dysfunction. Inflamm Res 2012; 61: 725–734.
23. Takahashi T, Anzai T, Yoshikawa T et al. Serum C-reactive protein elevation in left ventricular remodeling after acute myocardial infarction — role of neurohormones and cytokines. Int J Cardiol 2003; 88: 257–265.
24. Takahashi T, Anzai T, Kaneko H et al. Increased C–reactive protein expression exacerbates left ventricular dysfunction and remodeling after myocardial infarction. Am J Physiol Heart Circ Physiol 2010; 299: H1795–H1804.
25. Velazquez E, Francis G, Armstrong P et al. for the VALLIANT Registry. An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALLIANT Registry. Eur Heart J 2004; 25: 1911–1919.
26. Hanania G, Cambou J, Gueret P et al for the USIC 2000 Investigators. Management and in–hospital outcome of patients with acute myocardial infarction admitted to intensive care units at the turn of the century: results from the French nationwide USIC 2000 registry. Heart 2004; 90: 1404–1410.
27. Every N, Frederick P, Robinson M et al. A comparison of the National Registry of Myocardial Infarction 2 with the Cooperative Cardiovascular Project. J Am Coll Cardiol 1999; 33: 1886–1894.
28. Weir A, McMurray J, Velazquez E et al. Epidemiology of Heart Failure and Left Ventricular Systolic Dysfunction after Acute Myocardial Infarction: Prevalence, Clinical Characteristics, and Prognostic Importance. Am J Cardiol 2006; 97: 13–25.
29. Magnesium in Coronaries (MAGIC) Trial Investigators. Early administration of intravenous magnesium to high-risk patients with acute myocardial infarction in the Magnesium in Coronaries (MAGIC) Trial: a randomized controlled trial. Lancet 2002; 360: 1189–1196.
30. Agewall S. How should we evaluate an open artery in STEMI patients? Eur Heart J 2005; 26: 634–636.
31. Solomon A, Gersh B. The open artery hypothesis. Ann Rev Med 1998; 49: 63–76.
32. Stone G, Grines C, Browne K et al. Predictors of in-hospital and six month outcome after acute myocardial infarction in the reperfusion era: the Primary Angioplasty in Myocardial Infarction (PAMI) trial. J Am Coll Cardiol 1995; 25: 370–377.
33. Funaro S, La Torre G, Madonna M et al. Incidence, determinants, and prognostic value of reverse left ventricular remodelling after primary percutaneous coronary intervention: results of the Acute Myocardial Infarction Contrast Imaging (AMICI) multicenter study. Eur Heart J 2000; 30: 566–575.
34. De Servi S, Mariani M, Mariani G et al. C–reactive protein increase in unstable coronary disease: cause or effect? J Am Coll Cardiol 2005; 46: 1496–1502.
35. Pietila K, Harmoinen A, Jokinitty J et al. Serum C-reactive protein concentration in acute myocardial infarction and its relationship to mortality during 24 months of follow-up in patients under thrombolytic treatment. Eur Heart J 1996; 17: 1345–1349.
36. Tsakiris A, Marnelos P, Nearchou N et al. The influence of thrombolytic therapy on C-reactive protein in ST-segment elevation acute myocardial infarction. Hellenic J Cardiol 2006; 47: 218–222.
37. Ohlmann P, Jaquemin L, Morel O et al. Prognostic value of C-reactive protein and cardiac troponin I in primary percutaneous interventions for ST-elevation myocardial infarction. Am Heart J 2006; 152: 1161–1167.
38. Arruda-Olson A, Enriquez-Sarano M, Bursi F et al. Left ventricular function and C-reactive protein levels in acute myocardial infarction. Am J Cardiol 2010; 105: 917–921.
39. Brunetti N, Troccoli R, Correale M et al. C-reactive protein in patients with acute coronary syndrome: correlation with diagnosis, myocardial damage, ejection fraction and angiographic findings. Int J Cardiol 2006; 109: 248–256.
40. Suleiman M, Khatib R, Agmon Y et al. Early inflammation and risk of long-term development of heart failure and mortality in survivors of acute myocardial infarction — predictive role of C-reactive protein. J Am Coll Cardiol 2006; 47: 962–968.
41. Van de Werf F, Arolissino D, Betriu A et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2003; 24: 28–66.
42. Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2005. Stanowisko Polskiego Towarzystwa Diabetologicznego. Diabetologia Kliniczna 2004; 5 (Suppl. D): D1–D36.
43. Malmberg K, Ryden L, Hamsten A et al. Effects of insulin treatment on cause-specific 1–year mortality and morbidity in diabetic patients with acute myocardial infarction. DIGAMY Study Group. Diabetes insulin-glucose in acute myocardial infarction. Eur Heart J 1996; 17: 1337–1344.
44. Schiller N, Shah P, Crawford M et al. Recommendations for quantitation of the left ventricle by two–dimensional echocardiography. J Am Soc Echocardiogr 1989; 2: 358–367.
45. Lang R, Bierig M, Devereux B et al. Recommendations for chamber quantification. Eur J Echocardiography 2006; 7: 79–108.
46. Kasprzak JD, Hoffman P, Płońska E et al. Echokardiografia w praktyce klinicznej. Standardy Sekcji Echokardiografii Polskiego Towarzystwa Kardiologicznego 2007. Folia Cardiologica Excerpta 2007; 9: 409–434.
47. Otto C. The practice of Clinical Echocardiography. Saunders Elsevier, Philadelphia 2007.
48. Nagueh S, Appleton C, Gillebert T et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. Eur J Echocardiography 2009; 10: 165–193.
49. Makrygiannis S, Ampartzidou O, Zairis M et al. Prognostic usefulness of serial C-reactive protein measurements in ST-elevation acute myocardial infarction. Am J Cardiol 2013; 111: 26–30.
50. Mather A, Fairbairn T, Ball S et al. Reperfusion haemorrhage as determined by cardiovascular MRI is a predictor of adverse left ventricular remodelling and markers of late arrhythmic risk. Heart 2011; 97: 453–459.
51. Uehara K, Nomura M, Ozaki Y et al. High-sensitivity C-reactive protein and left ventricular remodeling in patients with acute myocardial infarction. Heart Vessels 2003; 18: 67–74.
52. Zebrack J, Anderson J. Should C-reactive protein be measured routinely during acute myocardial infarction? Am J Med 2003; 115: 735–737.
53. Mather A, Fairbairn T, Artis N. Relationship of cardiac biomarkers and reversible and irreversible myocardial injury following acute myocardial infarction as determined by cardiovascular magnetic resonance. Int J Cardiol 2013; 166: 458–464.
54. de Beer F, Hind C, Fox K et al. Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction. British Heart J 1982; 47: 239–243.
55. Minatoguchi T, Takemura G, Chen X et al. Acceleration of the healing process and myocardial regeneration may be important as a mechanism of improvement of cardiac function and remodeling by postinfarction granulocyte colony-stimulating factor treatment. Circulation 2004; 109: 2572–2580.
56. Theroux P, Armstrong P, Mahaffey K et al. Prognostic significance of blood markers of inflammation in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty and effects of pexelizumab, a C5 inhibitor: a substudy of the COMMA trial. Eur Heart J 2005; 26: 1964–1970.
57. Roes S, Kelle S, Kaandorp T et al. Comparison of myocardial infarct size assessed with contrast–enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction. Am J Cardiol 2007; 100: 930–936.
58. Olszowska M, Kostkiewicz M, Podolec P et al. Assessment of resting perfusion defect in patients with acute myocardial infarction: comparison of myocardial contrast echocardiography with contrast-enhanced magnetic resonance imaging. Kardiol Pol 2009; 67: 1013–1018.

59. Wita K, Filipecki A, Szydło K et al. Prediction of long-term outcome after primary percutaneous coronary intervention for acute myocardial infarction. Kardiol Pol 2010; 68: 393–400.
60. Damman P, Wichert J, Woudstra P et al. Multiple biomarkers at admission are associated with angiographic, electrocardiographic, and imaging cardiovascular mechanistic markers of outcomes in patients undergoing primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. Am Heart J 2012; 163: 783–789.
61. Celik T, Iyisoy A, Kursaklioglu H et al. The impact of admission C-reactive protein levels on the development of poor myocardial perfusion after primary percutaneous intervention in patients with acute myocardial infarction. Coron. Artery Dis 2005; 16: 293–299.
62. Ørn S, Manhenke C, Greve O et al. Microvascular obstruction is a major determinant of infarct healing and subsequent left ventricular remodelling following primary percutaneous coronary intervention. Eur Heart J 2009; 30: 1978–1985.
63. Mayr A, Klug G, Schocke M et al. Late microvascular obstruction after acute myocardial infarction: Relation with cardiac and inflammatory markers. Int J Cardiol 2012; 157: 391–396.
64. Festa A, D'Agostino R, Howard G et al. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000; 102: 42–47.
65. Otter W, Winter M, Doering W et al. C-reactive protein in diabetic and non-diabetic patients with acute myocardial infarction. Diabetes Care 2007; 12: 3080–3082.
66. Piestrzeniewicz K, Łuczak K, Goch H. Factors associated with C-reactive protein at the early stage of acute myocardial infarction in men. Cardiology J 2009; 16: 36–42.
67. Świątkiewicz I, Magielski P, Koziński M et al. Stężenie białka C-reaktywnego a pozawałowa dysfunkcja lewej komory u pacjentów z cukrzycą i bez cukrzycy. Pol Przegl Kardiol 2012; 14: 245–254.
68. Heo J, Park J, Kim J et al. Comparison of inflammatory markers between diabetic and nondiabetic ST segment elevation myocardial infarction. J Cardiol 2012; 60: 204–9.
69. Deedwania P, Kosiborod M, Barrett E et al. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2008; 117: 1610–1619.
70. Ishihara M, Kagawa E, Inoue I et al. Impact of admission hyperglycemia and diabetes mellitus on short- and long-term mortality after acute myocardial infarction in the coronary intervention era. Am J Cardiol 2007; 99: 1674–1679.
71. Pinto D, Kirtane A, Pride Y et al. Association of blood glucose with angiographic and clinical outcomes among patients with ST-segment elevation myocardial infarction (from CLARITY-TIMI-28 study). Am J Cardiol 2008; 10: 303–307.
72. Świątkiewicz I, Gierach J, Magielski P et al. Zależność pomiędzy wyjściowym stężeniem białka C-reaktywnego a dysfunkcją skurczową lewej komory przy wypisie ze szpitala u pacjentów z pierwszym w życiu ostrym zawałem serca leczonych przezskórną interwencją wieńcową. Folia Cardiol Excerpta 2011; 6: 99–108.
73. Festa A, D'Agostino R, Howard G et al. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000; 102: 42–47.
74. Sutherland J, McKinley B, Eckel R. The metabolic syndrome and inflammation. Metab Syndr Relat Disord 2004; 2: 82–104.
75. Haeck J, Verouden N, Kuijt W et al. Comparison of usefulness of N–terminal pro–brain natriuretic peptide as an independent predictor of cardiac function among admission cardiac serum biomarkers in patients with anterior wall versus nonarterior wall ST–segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol 2010; 105: 1065–1069.
76. van Diepen S, Roe M, Lopes R et al. Baseline NT-proBNP and biomarkers of inflammation and necrosis in patients with ST-segment elevation myocardial infarction: insights from the APEX-AMI trial. J Thromb Thrombolysis 2012; 34: 106–113.
77. Khan H, Alhomida A, Sobki S et al. Blood cell counts and their correlation with creatinine kinase and C–reactive protein in patients with acute myocardial infarction. Int J Clin Exp Med 2012; 5: 50–55.
78. Chia S, Nagurney J, Brown D et al. Association of leukocyte and neutrophil counts with infarct size, left ventricular function and outcomes after percutaneous coronary intervention for ST-elevation myocardial infarction. Am J Cardiol 2009; 103: 333–337.
79. Jolly S, Kane W, Hook B et al. Reduction of myocardial infarct size by neutrophil depletion: effect of duration of occlusion. Am Heart J 1986; 112: 682–690.
80. Van Melle J, van der Vleuten, Hummel Y et al. Predictive value of tissue Doppler imaging for left ventricular ejection fraction, remodeling, and infarct size after percutaneous coronary intervention for acute myocardial infarction. Eur J Echocardiography 2010; 11: 596–601.
81. Ottervanger J, van't Hof A, Reiffers S et al. Long-term recovery of left ventricular function after primary angioplasty for acute myocardial infarction. Eur Heart J 2001; 22: 785–790.
82. Parodi G, Memisha G, Carabba N et al. Prevalence, predictors, time course, and long-term clinical implications of left ventricular functional recovery after mechanical reperfusion for acute myocardial infarction Am J Cardiol 2007; 100: 1718–1722.
83. Solomon S, Glynn R, Greaves S et al. Recovery of ventricular function after myocardial infarction in the reperfusion era: the healing and early afterload reducing therapy study. Ann Int Med 2001; 134: 451–458.
84. Sheiban I, Fragasso G, Rosano G et al. Time course of determinants of left ventricular recovery after primary angioplasty in patients with acute myocardial infarction. J Am Coll Cardiol 2001; 38: 464–471.
85. Antoni M, Mollema S, Atary J et al. Time course of global left ventricular strain after acute myocardial infarction. Eur Heart J 2010; 31: 2006–2013.
86. Olszowska M, Tracz W, Kostkiewicz M et al. Predictive factors of myocardial reperfusion in patients with anterior wall acute myocardial infarction. Cardiology J 2008; 15: 57–62.
87. Świątkiewicz I, Magielski P, Woźnicki M et al. Occurence and predictors of left ventricular systolic dysfunction at hospital discharge and in long--term follow-up sfter acute myocardial infarction treated with primary percutaneous coronary intervention. Kardiol Pol 2012; 70: 157–163.
88. Ndrepepa G, Mehili J, Martinoff S et al. Evolution of left ventricular ejection fraction and its relationship to infarct size after acute myocardial infarction. J Am Coll Cardiol 2007; 50: 149–156.
89. Streb W, Duszańska A, Stabryła-Deska J et al. The comparison of contrast echocardiography and tissue Doppler imaging for evaluation of reperfused myocardium in patients with acute anterior myocardial infarction. Cardiol J 2008; 6: 548–554.
90. Baks T, van Geuns R, Biagini E et al. Recovery of left ventricular function after primary angioplasty for acute myocardial infarction. Eur Heart J 2005; 26: 1070–1077.
91. Bolognese L, Carrabba N, Parodi G et al. Impact of microvascular dysfunction on left ventricular remodeling and long–term clinical outcome after primary coronary angioplasty for acute myocardial infarction. Circulation 2004; 109: 1121–1126.
92. Ferreira R. The reduction of infarct size — forty years of research. Rev Port Cardiol 2010; 29:1037–1053.
93. Olszowska M, Tracz W, Hlawaty M. The prognostic value of contrast echocardiography in the prediction of the recovery of left ventricular function in patients with acute anterior myocardial infarction. Kardiol Pol 2006; 64: 455–461.
94. Ezekowitz J, Armstrong P, Granger C et al. Predicting chronic left ventricular dysfunction 90 days after ST-segment elevation myocardial infarction: An Assessment of Pexelizumab in Acute Myocardial INfarction (APEX–AMI) Substudy. Am Heart J 2010; 160: 272–278.
95. Taglieri N, Saia F, Guiducci V et al. Left ventricular function after ST-elevation myocardial infarction in patients treated with primary percutaneous coronary intervention and abciximab or tirofiban (from FATA Trial). Am J Cardiol 2009; 103: 785–790.
96. Hassan A, Bergheanu S, Hasan-Ali H. Usefullness of peak troponin-T to predict infarct size and long-term outcome in patients with first acute myocardial infarction after primary percutaneous coronary intervention. Am J Cardiol 2009; 103: 779–84.
97. Cruz-Gonzales I, Chia S, Raffell O et al. Hyperglycemia on admission predicts larger infarct size in patients undergoing percutaneous coronary intervention for acute ST-segment elevation myocardial infarction. Diabetes Res Clin Pract 2010; 88: 97–102.
98. Htay T, Mehta D, Heo J et al. Left ventricular function in patients with type 2 diabetes mellitus. Am J Cardiol 2005; 95: 798–801.
99. von Bibra H, Sutton M. Impact of diabetes on postinfarction heart failure and left ventricular remodeling. Curr Heart Fail Rep 2011; 8: 242–251.