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ORIGINAL RESEARCH

Biomarkers of Systemic Versus Local Inflammation During the Acute Phase of Myocardial Infarction, as Predictors of Post-infarction Heart Failure

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ABSTRACT

Background: The aim of this study was to investigate the correlation between serum biomarkers of left ventricular dysfunction and systemic inflammation in the first days after the acute episode, and to investigate their role for early identification of patients at high risk for post-infarction heart failure. **Materials and methods:** In total, 123 subjects admitted to the Intensive Cardiovascular Care Unit of the Cardiology Clinic of the Târgu Mureș County Clinical Emergency Hospital, Romania, with acute myocardial infarction were retrospectively analyzed in this study. Based on the level of NT-proBNP, the study population was divided into 2 groups: Group 1 (n = 92), with NT-proBNP <3,000 pg/mL, and Group 2 (n = 31), with NT-proBNP >3,000 pg/mL. **Results:** Biomarkers reflecting systemic inflammation presented significantly higher values in patients with elevated NT-proBNP (hs-CRP – 12.3 ± 8.9 mg/L vs. 3.6 ± 6.7 mg/L, p <0.0001, and interleukin 6 – 27.6 ± 30.7 pg/mL vs. 8.6 ± 6.2 pg/mL, p <0.0001). However, cell adhesion molecules VCAM and ICAM were not significantly different between the groups. Patients in Group 2 presented significantly higher rates of major cardiovascular events and rehospitalizations in the first year after the acute coronary event, with 13.33% event rate for patients in Group 2 compared to 8.7% in Group 1 (p <0.05). **Conclusions:** Serum biomarkers of ventricular dysfunction are strongly associated with systemic inflammation and ventricular impairment in the immediate phase after an acute myocardial infarction. Systemic inflammation has a higher impact on the clinical outcomes and progression to heart failure than the local coronary inflammation expressed by cell adhesion molecules.

Keywords: acute myocardial infarction, heart failure, systemic inflammation, local inflammation, biomarkers

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INTRODUCTION

It is well accepted that systemic inflammation has a major role in the progression of atheromatous plaques. Many studies have indicated that patients with acute coronary syndromes have an elevated systemic inflammatory status, which is directly correlated with the vulnerability of atherosclerotic plaques.[1] Moreover, myocardial inflammation may lead to myocarditis, heart failure, cardiac arrhythmias, acute coronary syndrome, or sudden cardiac death.[2] It has been described that a persistently increased inflammatory status associated with other non-cardiovascular diseases, including periodontal diseases, or with alterations of gut microbiota, leads to a higher risk of cardiovascular events.[3,4]

In patients with acute myocardial infarction (AMI), serum levels of C-reactive protein (CRP) increase after 4 hours from onset, reaching peak levels in 2–4 days, and then normalize at 7 days after the acute myocardial ischemia episode. A persistently elevated inflammatory status after this period is strongly linked to an increased risk of complications or deleterious ventricular remodeling.[5]

A recently published study has demonstrated a strong correlation between serum levels of CRP in the acute phase of myocardial infarction and the severity of coronary lesions ($r = 0.3$, $p = 0.05$), which is inversely correlated with the left ventricular ejection fraction (LVEF) ($r = -0.43$, $p = 0.05$).[6] Currently, it is acknowledged that CRP is a specific biomarker for systemic inflammation, while N-terminal pro-brain natriuretic peptide (NT-proBNP) serves as a reliable biomarker of ventricular dysfunction.[7]

These observations illustrate the major role of systemic inflammation in the development of myocardial infarction and, nonetheless, its role in the myocardial reparative and proliferative process after the acute episode.[7] A recent clinical study which included 204 patients with AMI has revealed that an elevated CRP level was a precise predictor for ventricular dysfunction after the acute coronary event (odds ratio 1.47, $p = 0.01$).[7]

The influence of an elevated inflammatory response following an AMI has been extensively studied. However, little is known about the impact of inflammation on cardiac function immediately after the acute episode. The cardiac myocyte disturbance cause by ischemia and inflammation may lead to left ventricular remodeling, which is associated with cardiac dilation and heart failure.[8]

The aim of this study was to investigate the correlation between serum biomarkers indicative for left ventricular dysfunction and for systemic inflammation in the first days after the acute episode, and to investigate their role for early identification of patients at high risk for developing heart failure after AMI.

MATERIALS AND METHODS

We conducted a retrospective study including 123 consecutive subjects admitted to the Intensive Care Unit of the Cardiology Clinic of the Târgu Mureș County Clinical Emergency Hospital, Romania, with AMI. In all patients, full blood cell count alongside biochemical determinations for LDL-cholesterol, HDL-cholesterol, triglycerides, glycemia, renal function parameters (creatinine, urea), uric acid were evaluated. All patients underwent evaluation of serum levels of NT-proBNP and inflammatory biomarkers, including cell adhesion molecules (E-selectin, hs-CRP, IL-6, VCAM, ICAM, Apo B) and cardiac enzymes.

Demographic data, hemodynamic characteristics (cardiogenic shock, LVEF), number of hospitalization days in the intensive cardiovascular care unit, total number of hospitalization days as well as comorbidities and risk factors (hypertension, chronic kidney disease, smoking status, stroke, previous myocardial infarction, peripheral arterial disease, atrial fibrillation, obesity, pulmonary disease) were extracted from patient medical records and registered in the study database.

Based on standard criteria, patients were diagnosed with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (nSTEMI) and underwent primary percutaneous intervention (PCI) according to the guidelines of the European Society of Cardiology. Angiographic characteristics, such as localization of culprit lesion, post-procedural TIMI flow, or multivessel PCI, were recorded in the database. Percutaneous transluminal coronary angiography and coronary revascularization were performed in all indicated cases with the amount of contrast agent personalized for each patient.

Left ventricular function was assessed with the use of transthoracic echocardiography, which was performed by an experienced cardiologist with a Philips CX50 ultrasound system (Philips Medical System Netherlands BV) with a S5-1 transducer.

Statistical analysis was performed with Graph Pad Prism 8.0 software after all data was verified. Statistical significance was set at a p value of 0.05.

Based on the level of NT-pro-BNP, the study population was divided into two main groups: Group 1 – patients with NT-proBNP <3,000 pg/mL, and Group 2 – patients with NT-proBNP >3,000 pg/mL.

All study procedures were conducted in accordance with the principles of the Declaration of Helsinki. All patients have signed a written informed consent in regards to the use of their medical data for research purposes upon hospital admission, and the research was approved by the local ethics committee of the hospital in which the study was conducted.

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY POPULATION

This study included 123 patients with AMI, 69.1% (n = 85) with STEMI and 30.89% (n = 38) with nSTEMI. The mean age was 62.93 ± 10.99 years, and 74.79% (n = 92) of the patients were males. Mean weight of the study population was 86.30 ± 15.96 kg.

Twenty-one patients from Group 1 and 4 patients from Group 2 were active smokers, while a majority of 52.84% (n = 65) were hypertensive. There was no statistically significant difference between the two study groups regarding age, comorbidities such as obesity and diabetes, or history of myocardial infarction and stroke. Baseline characteristics, comorbidities, and risk factors of the two study groups are presented in Table 1.

HEMODYNAMIC AND ANGIOGRAPHIC CHARACTERISTICS

Assessment of hemodynamic status revealed a lower LVEF and a higher Killip class for Group 2, where NT-proBNP levels were significantly higher. The average value of LVEF was 50.45% in Group 1 and 42.87% in Group 2 (p <0.0001). With regard to Killip classification, 76 patients (82.6%) from Group 1 were in Killip class I, 13 (14.13%) in Killip class II, and 3 (3.26%) in Killip class III. In Group 2, 18 patients (58.06%) were in Killip class I, 6 (19.35%) in Killip class II, and 7 (22.58%) in Killip class III. Moreover, patients with an elevated NT-proBNP level presented significantly higher frequency of cardiogenic shock, as well as a longer periods of hospitalization. As expected, patients with high levels of NT-proBNP had a longer duration of stay in the intensive cardiovascular care unit and a longer total duration of hospitalization.

Hemodynamic characteristics, LVEF, and duration of hospital stay are presented in Table 2.

Angiographic analysis revealed a decreased TIMI flow and a higher incidence of multivessel disease in patients with elevated levels of NT-proBNP. In both groups, the culprit lesion was located predominantly in the left anterior descending artery (LAD) (in 46% patients from Group 1 and 58% patients from Group 2), however, without a statistically significant difference between the groups (Table

TABLE 1. Baseline characteristics, comorbidities, and risk factors in the study population

Parameter	Total (n = 123)	Group 1 (n = 92)	Group 2 (n = 31)	p value
Male gender, n (%)	92 (74.79%)	62 (76,54%)	30 (71.43%)	0.6618
Female gender, n (%)	31 (25.20%)	19 (23.46%)	12 (28.57%)	0.6618
Age, years(mean ± SD)	62.93 ± 10.99	62.22 ± 11.41	65.03 ± 9.51	0.2596
Smoking status, n (%)	25 (20.32%)	21 (22.82%)	4 (12.90%)	0.3067
STEMI, n (%)	85 (69.1%)	64 (69.56%)	21 (67.74%)	0.8493
NSTEMI, n (%)	38 (30.89%)	28 (30.43%)	10 (32.35%)	0.8493
Killip class 1, n (%)	94 (76.42%)	76 (82.6%)	18 (58.06%)	0.0016
Killip class 2, n (%)	19 (15.14%)	13 (14.13%)	6 (19.35%)	0.0016
Killip class 3, n (%)	10 (8.13%)	3 (3.26%)	7 (22.58)	0.0016
Hypertension, n (%)	65 (52.84%)	51 (55.43%)	14 (45.16%)	0.4061
Diabetes mellitus, n (%)	14 (11.38%)	8 (8.69%)	6 (19.35%)	0.1149
Obesity, n (%)	10 (8.13%)	8 (8.69%)	2 (6.45%)	0.9999
Renal chronic disease, n (%)	2 (1.62%)	1 (1.08%)	1 (3.22%)	0.1562
Previous MI, n (%)	4 (3.25%)	1 (1.08%)	3 (9.67%)	0.0551
Previous stroke (%)	9 (29.13%)	6 (6.52%)	3 (9.67%)	0.6904
History of peripheral obliterative arteriopathy (%)	5 (4.06%)	2 (2.17%)	3 (9.67%)	0.1013
History of atrial fibrillation (%)	8 (6.5%)	5 (5.43%)	3 (9.67%)	0.4143
History of pulmonary disease (%)	4 (3.25%)	2 (2.17%)	2 (6.45%)	0.2634

TABLE 2. Hemodynamic characteristics and duration of hospital stay in the study population

Parameter	Group 1 (n = 92)	Group 2 (n = 31)	p value
Left ventricular ejection fraction, mean ± SD (95% CI)	50.45 ± 5.209 (49.37–51.52)	42.87 ± 5.315 (40.92–44.82)	<0.0001
Intensive cardiovascular care unit hospitalization days, mean ± SD (95% CI)	1.793 ± 0.6383 (1.661–1.926)	2.419 ± 0.6204 (2.192–2.647)	<0.0001
Total hospitalization days, mean ± SD (95% CI)	6.891 ± 0.7025 (6.746–7.037)	8.484 ± 1.639 (7.886–9.082)	<0.0001
Killip class 1, n (%)	76 (82.6%)	18 (58.06%)	0.001
Killip class II, n (%)	13 (14.13%)	6 (19.53%)	
Killip class III, n (%)	3 (3.26%)	7 (22.58%)	
Killip class IV (cardiogenic shock), n (%)	1 (0.1%)	6 (19.35%)	0.001

3). The culprit lesion was located in the circumflex artery in 30.4% of patients from Group 1 vs. 19.3% of patients from Group 2. Location of culprit lesion in the LAD was associated with a more severe ventricular dysfunction, which may be related to the larger territory of myocardial distribution of the LAD.

SERUM BIOMARKERS AND LEFT VENTRICULAR DYSFUNCTION

The mean NT-proBNP levels were 744.5 ± 29.56 pg/L in Group 1 and 12.310 ± 8.930 pg/L in Group 2 (p <0.0001). Serum levels of biomarkers of myocardial necrosis, represented by peak creatine kinase (CK), were significantly higher in patients with high NT-proBNP levels (Group 1 – 940.6 ± 892.6 U/L vs. Group 2 – 2,896 ± 6,074 U/L p = 0.003), demonstrating a clear correlation between ventricular dysfunction and extension of myocardial necrosis (Figure 1).

Biomarkers reflecting systemic inflammation presented significantly higher levels in patients with elevated NT-proBNP, both for high-sensitivity CRP (hs-CRP) (12.3 ± 8.9 mg/L vs. 3.6 ± 6.7 mg/L, p <0.0001) and interleukin 6 (27.6 ± 30.7 pg/mL vs. 8.6 ± 6.2 pg/mL, p <0.0001), being directly correlated with ventricular dysfunction (r = 0.45) (Figure 2). At the same time, hs-CRP presented a very good correlation with NT-proBNP, indicating the strong link between inflammation and ventricular dysfunction (Figure 3).

IMPACT OF LEFT VENTRICULAR DYSFUNCTION ON THE RATE OF CARDIOVASCULAR EVENTS

Patients in Group 2 presented significantly higher rates of major cardiovascular events and rehospitalizations in the first year after the acute coronary event. The rate of major cardiovascular events (defined as reinfarction, stroke, or death) at one year after the AMI was 13.33% for patients

TABLE 3. Angiographic characteristics

Parameter	Group 1 (n = 92)	Group 2 (n = 31)	p value
Multivessel coronary disease, n (%)	10 (10.89%)	14 (45.16%)	<0.0001
Culprit artery			
LAD, n (%)	43 (46.73%)	18 (58.06%)	0.4426
ACX, n (%)	28 (30.43%)	6 (19.35%)	
RCA, n (%)	21 (22.82%)	7 (22.58%)	
TIMI flow			
TIMI I, n (%)	0	4 (12.90%)	0.0003
TIMI II, n (%)	19 (20.65%)	11 (35.48%)	
TIMI III, n (%)	73 (79.34%)	16 (51.61%)	

LAD – left anterior descending artery; ACX – circumflex artery; RCA – right coronary artery

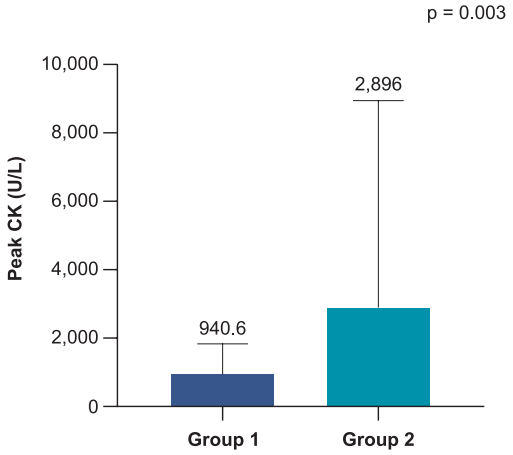

FIGURE 1. Serum levels of peak creatine kinase in the study groups

in Group 2 compared to 8.7% in Group 1. Hospitalization rates at one year were also higher for patients from Group 2 (12.9% vs. 7.6%). The mortality rate was significantly higher in patients with increased NT-proBNP levels (6.45% in Group 2 vs. 2.17% in Group 1). The incidence of major cardiovascular events in the study groups is illustrated in Figure 4.

DISCUSSIONS

It is widely known that patients with marked inflammatory status are at greater risk of developing acute or chronic coronary syndromes. Hence, systemic inflammation indicated by a high serum titer of hs-CRP has a strong predictive value for cardiovascular risk. A persistently elevated inflammatory status after an acute coronary event has been associated with a higher rate of recurrent cardiovascular events. Several studies have concluded that a high level of inflammatory biomarkers is a strong predictor for major adverse cardiac events.[9]

Moreover, a pronounced inflammatory activity is related to unsatisfactory results after primary revascularization, consequently impacting ventricular function. This was also demonstrated in this study by a significant inverse correlation between increased NT-proBNP levels and the rate of patients presenting TIMI III flow after the

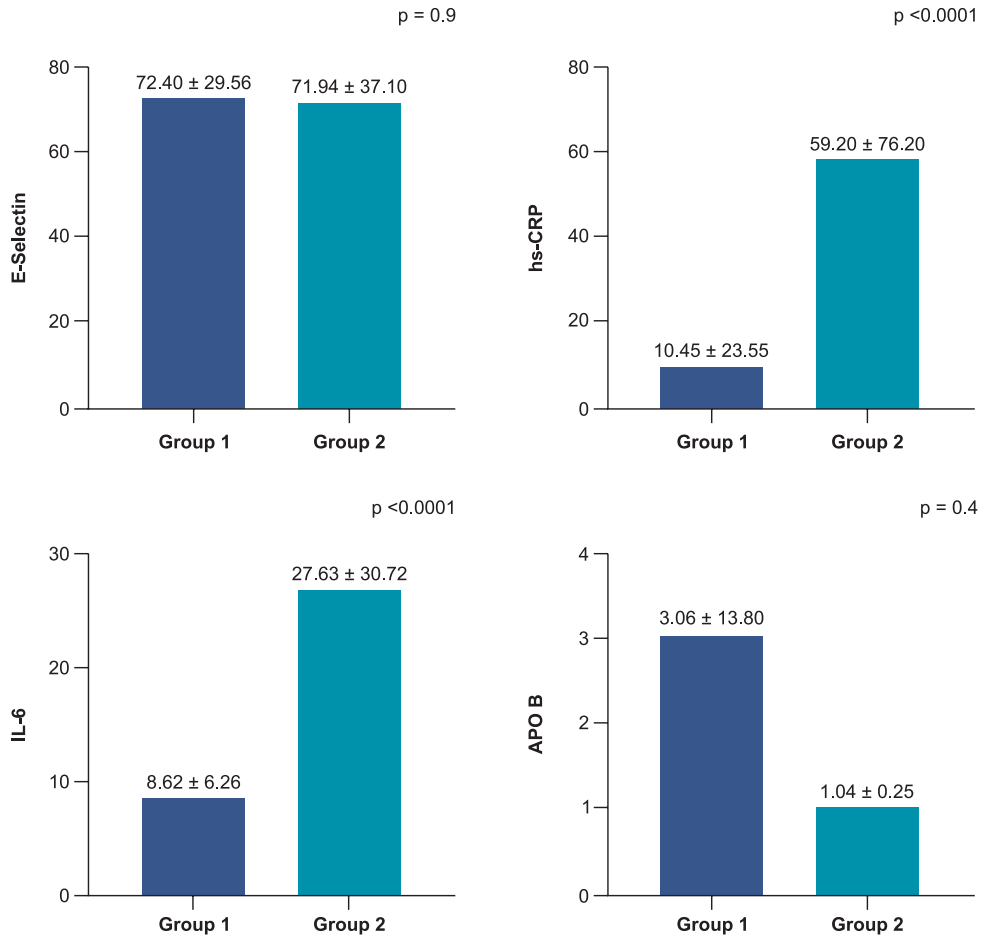

FIGURE 2. Biomarkers reflecting systemic inflammation

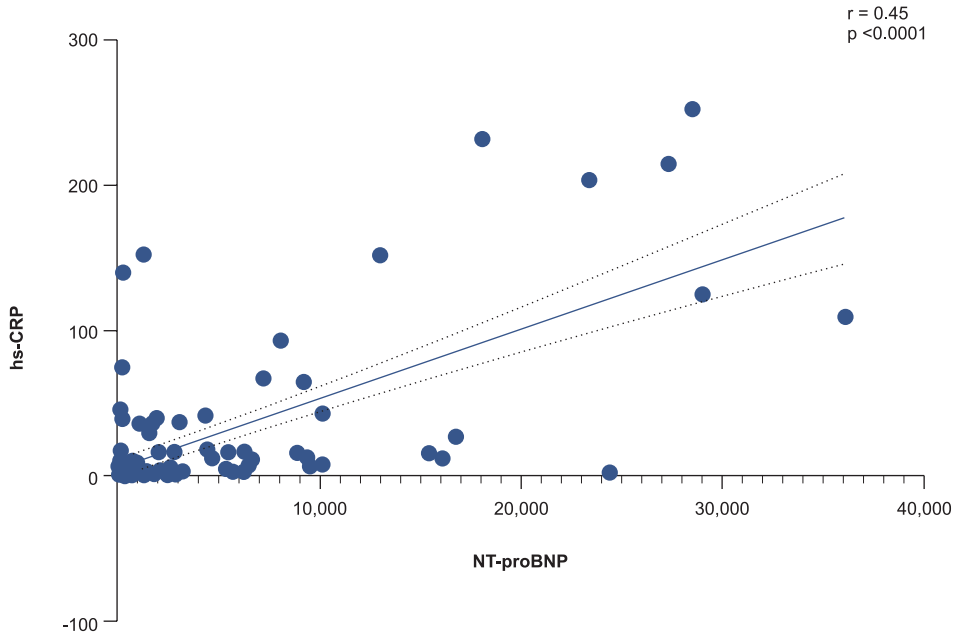

FIGURE 3. Correlation between hs-CRP and NT-proBNP levels

primary revascularization procedure (51.6% vs. 79.3%, p = 0.003).

Adhesion molecules such as VCAM and ICAM, reflect endothelial dysfunction in a higher extent compared to markers for systemic inflammation. A study conducted on 80 patients by Macías *et al.* has demonstrated that high levels of cell adhesion molecules are present in the acute phase of a coronary syndrome, without notable differences between the study lot and controls at 10 days following the acute event.[9] This observation was consistent with the results of our study, which found no significant difference in VCAM and ICAM values between the study groups (p = 0.3 for VCAM and p = 0.2 for ICAM). This indicates that adhesion molecules are not reliable biomarkers for the assessment of systemic inflammation, even though they may be useful to indicate the severity of endothelial dysfunction associated with the rupture of vulnerable atherosclerotic plaques.

In line with these observations, our study revealed a statistically significant association between inflammatory biomarkers represented by hs-CRP, IL-6, and E-selectin, and NT-proBNP levels in patients suffering from a myocardial infarction. Also, patients with severe left ventricular dysfunction after an AMI have higher serum level of inflammatory biomarkers, while the level of biomarkers reflecting endothelial dysfunction was not

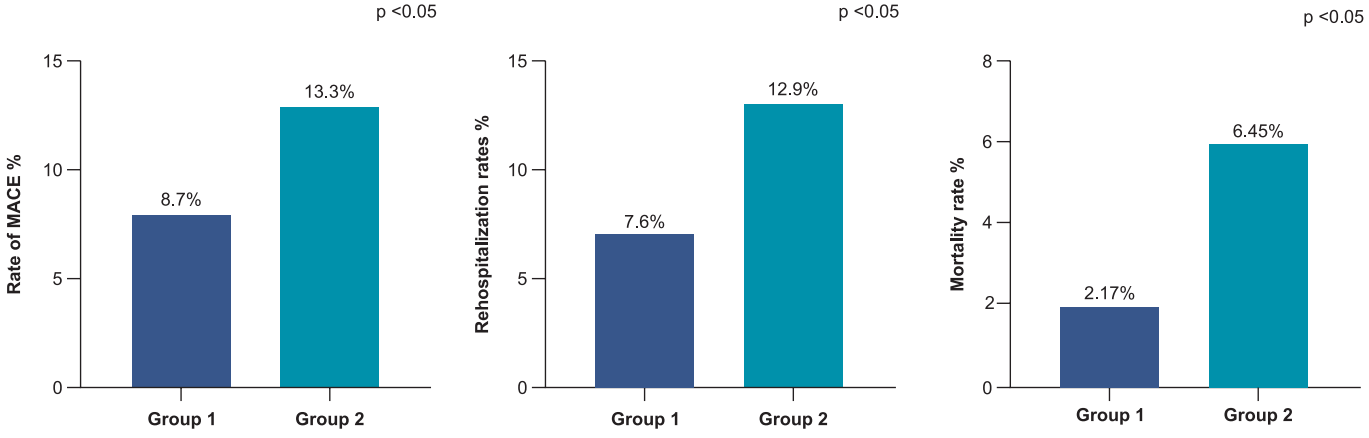

FIGURE 4. The rate of major adverse cardiovascular events, rehospitalization, and mortality at one year

significantly different between groups. This indicated a greater contribution of the systemic inflammatory status than the local one.

CONCLUSIONS

Serum biomarkers of ventricular dysfunction are strongly associated with systemic inflammation and ventricular impairment in the immediate phase following an acute myocardial infarction. At the same time, biomarkers associated with heart failure are strongly correlated with a culprit lesion located in the LAD and with a longer hospitalization period. Inflammatory biomarkers are highly correlated with the biomarkers of ventricular dysfunction in patients suffering from AMI. In contrast, adhesion molecules are not directly associated with ventricular function. All these indicate that systemic inflammation has a higher impact on clinical outcomes and progression to heart failure compared to the local inflammation in the coronary circulation.

CONFLICT OF INTEREST

Nothing to declare.

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