

CLINICAL INVESTIGATIONS

C-reactive protein during and after myocardial infarction in relation to cardiac injury and left ventricular function at follow-up

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Background: Acute myocardial infarction (MI) invokes a large inflammatory response, which contributes to myocardial repair.

Hypothesis: We investigated whether C-reactive protein (CRP) measured during MI vs at 1 month follow-up improves the prediction of left ventricular (LV) function.

Methods: We prospectively enrolled 131 consecutive patients with acute MI and without non-cardiovascular causes of inflammation. We correlated admission and peak levels of CRP during hospitalization and high-sensitivity (hs) CRP at 1 month follow-up with markers of cardiac injury. Clinical follow-up and echocardiography for LV function were performed at a mean of 17 months.

Results: Median CRP levels were 1.89 mg/L on admission with MI, peaked to 12.10 mg/L during hospitalization and dropped to 1.24 mg/L at 1 month. Although admission CRP levels only weakly correlated with ejection fraction in the acute phase of MI (coefficient -0.164 , $P = 0.094$), peak CRP was significantly related to ejection fraction (coefficient -0.4 , $P < 0.001$), hsTroponin T (0.389 , $P < 0.001$), and white blood cell count (0.389 , $P < 0.001$). hsCRP at 1 month was not related to the extent of acute cardiac injury. These findings were replicated in an independent cohort of 57 patients. Peak CRP predicted LV dysfunction at follow-up (OR 11.0, 3.1-39.5 per log CRP, $P < 0.001$), persisting after adjustment for infarct size (OR 5.1, 1.1-23.6, $P = 0.037$), while hsCRP at 1 month was unrelated to LV function at follow-up.

Conclusions: hsCRP 1 month post-MI does not relate to acute cardiac injury or LV function at follow-up, but we confirm that peak CRP is an independent predictor of LV dysfunction at follow-up.

KEYWORDS

acute coronary syndrome, myocardial infarction, inflammation, C-reactive protein

1 | BACKGROUND

Acute myocardial infarction (MI) results in an inflammatory response involved in myocardial repair.¹ C-reactive protein (CRP), an acute phase reactant as downstream marker of inflammation, has been shown to correlate with the extent of cardiac injury in the acute phase of MI.^{2,3} Although the resolution of post-MI inflammation is generally expected after 2 to 4 weeks, a prolonged inflammatory phase can occur.⁴ However, it is unknown whether the extent of acute cardiac

injury influences residual high-sensitivity (hs)CRP levels at 1 month post-MI. Low-grade inflammation measured by hsCRP measured at least 1 month after MI is indeed an established predictor of recurrent cardiovascular events.⁵⁻⁸ Recently, inhibition of IL-1 β with canakinumab in patients with increased hsCRP at least 1 month after MI has shown to improve outcome.⁹ The aim of this study was therefore to measure CRP not only during hospitalization for acute MI, but also at 1 month follow-up, and investigate its association with markers of acute cardiac injury and left ventricular function at follow-up.

2 | METHODS

2.1 | Patients and follow-up

We prospectively enrolled consecutive patients admitted to our department with acute MI (MI study). The study protocol was approved by the institution's ethical committee (Belgian trial number B322201214942) and all patients provided informed consent. The diagnosis of MI was made according to the third universal definition of MI.¹⁰ Patients with Killip class III or IV, infection, inflammatory disease, malignancy, end-stage renal disease, end-stage pulmonary disease, or patients treated with immunomodulatory drugs were excluded. Baseline patient characteristics and angiographic details were recorded. During hospitalization, serial high-sensitivity troponin T, MB-creatinine kinase (CK-MB), and conventional CRP were measured daily. The extent of cardiac injury was assessed by the peak in troponin T or CK-MB release, and the inflammatory response by

peak CRP during hospitalization.¹¹ Global left ventricular function (LV function) was assessed on admission by transthoracic echocardiography using a Vivid E9 (GE Healthcare, Diegem, Belgium). Blood sampling for hsCRP was performed at 1 month follow-up. Transthoracic echocardiography was performed at 1 year follow-up. Clinical follow-up was performed up to 2 years. LV dysfunction was defined as ejection fraction of 45% or below. Major adverse cardiovascular events (MACE) were defined as cardiovascular death, recurrent MI, recurrent ischemia or stroke.

2.2 | Replication cohort

A second group of patients from the Study on Aerobic INTERVAL EXercise in Coronary Artery Disease (SAINTEX-CAD), in which the effect of cardiac rehabilitation on aerobic exercise capacity was evaluated in patients after MI, served as a replication cohort.¹² In this cohort, serial CK-MB and CRP during hospitalization, hsCRP at 1 month after the

TABLE 1 Baseline patient characteristics on admission with MI

	MI cohort (n = 131)	SAINTEX cohort (n = 57)	P value
Age, mean ± S.D.	63 ± 11	58 ± 8	< 0.001
Sex, male, n (%)	100 (76)	53 (93)	0.007
Body mass index ± S.D.	27.8 ± 5.4	28.8 ± 4.6	0.243
Medical history, n (%)			
Current smoker	49 (37)	23 (40)	0.745
Hypertension	59 (45)	30 (53)	0.346
Diabetes	18 (14)	10 (18)	0.510
Prior MI	12 (9)	2 (4)	0.234
Prior revascularization	13 (10)	8 (14)	0.453
Medication on admission, n (%)			
Aspirin	34 (26)	9 (17)	0.187
Beta-blocker	35 (27)	12 (21)	0.467
ACE-inhibitor	19 (15)	9 (16)	0.826
Angiotensin receptor antagonist	10 (8)	3 (5)	0.757
Statin	41 (31)	16 (28)	0.733
MI presentation			
ST-elevation, n (%)	61 (47)	49 (86)	<0.001
Anterior infarction, n (%)	54 (41)	22 (39)	0.750
EF on admission ≤ 45%, n (%)	23 (22)	17 (39)	0.043
CABG, n (%)	11 (8)	2 (4)	0.350
Three-vessel disease, n (%)	27 (21)	8 (14)	0.317
CRP levels			
CRP, admission (IQR) (mg/L)	1.89 (0.97-4.45)	1.85 (0.80-5.08)	0.930
CRP, peak (IQR) (mg/L)	12.10 (6.45-30.40)	18.80 (7.20-40.00)	0.141
hsCRP, 1 mo (IQR) (mg/L)	1.24 (0.47-2.43)	1.57 (0.71-3.34)	0.051
Cardiac injury markers			
CK-MB (IQR) (μg/L)	20.1 (6.6-70.2)	83.7 (19.3-142.9)	<0.001
hsTnT (IQR) (μg/L)	1.100 (0.242-2.920)		
Clinical follow-up			
LV dysfunction, n (%)	14 (13)	4 (7)	0.280
MACE, n (%)	13 (10)	6 (11)	1.000

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; CK-MB, creatine kinase-MB; CRP, C-reactive protein; CRP, C-reactive protein; EF, ejection fraction, HF, heart failure; hsTnT, high-sensitivity troponin T; LV dysfunction, left ventricular dysfunction; MACE, major adverse cardiovascular events; MI, myocardial infarction. Values are mean ± S.D. or median with interquartile range (IQR).

index event, LV function assessed by transthoracic echocardiography at 4 months, and clinical follow-up was available in 57 post-MI patients as previously described.¹²

2.3 | Measurement of CRP

Levels of CRP during hospitalization were assessed using a third generation C-reactive protein (CRPL3) assay on Cobas C702, with a measuring range of 0.3 to 350 mg/L allowing quantification of high CRP values. hsCRP at follow-up was measured using the Cardiac C-reactive Protein High Sensitive (CRPHS) assay on Cobas Integra 400 plus, with a measuring range of 0.1 to 20 mg/L and increased accuracy at low values.

2.4 | Statistical analysis

Parametric and nonparametric tests were used according to the distribution of the variables. The correlation between continuous variables was assessed using the Pearson correlation coefficient. Peak CRP and hsCRP at follow-up were first log-transformed because they were not normally distributed. In univariable and multivariable regression analyses, we report the standardized coefficient Beta. To compare differences in event-free survival, the Kaplan-Meier curve was calculated and the log-rank test was used to compare groups. Statistical analyses were performed using SPSS Statistics 24.0 (IBM, New York, New NY). Analysis of the receiver operating characteristic (ROC) curve and determination of the optimal cut-off point using the Youden index was performed in the R-based easyROC 1.3.

3 | RESULTS

3.1 | Patients

We prospectively included 161 consecutive patients with MI between October 2013 and April 2015 (MI cohort) (Table 1). Thirty patients were excluded because of infection, inflammatory disease or because no blood sample was available at 1 month. Three patients were lost to follow-up and 111 patients (85%) completed echocardiographic follow-up at 1 year. The validation study (SAINTEX cohort) consisted of 57 patients (Table 1). Six patients in this study developed an infection or inflammatory disease during hospitalization influencing CRP levels, and were not included in the final analysis. Clinical follow-up was available in all patients and 56 patients (98%) completed echocardiographic follow-up. Compared to the MI cohort, the SAINTEX patients were younger and more frequently male, and had more frequently ST-elevation MI and a larger infarct size as measured by peak CK-MB.

3.2 | CRP measurements

In the MI cohort, median CRP levels were 1.89 mg/L (IQR 0.97-4.45 mg/L) on admission for MI, and peaked to 12.10 mg/L (IQR 6.45-30.40 mg/L) during hospitalization ($P < 0.001$, Figure 1A). At follow-up, hsCRP levels dropped to 1.24 mg/L (IQR 0.47-2.43 mg/L)

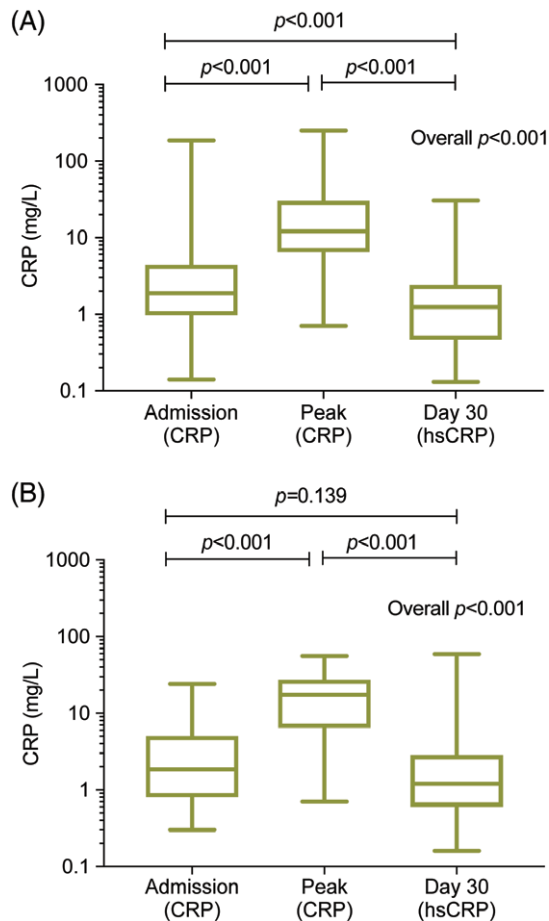


FIGURE 1 A, Temporal pattern of CRP levels on admission with MI, peak levels, and hsCRP levels at 30-days follow-up in the MI cohort. B, A similar temporal pattern was observed in the SAINTEX cohort, although the difference between admission CRP levels and 30-day hsCRP was not significant

at 1 month. A similar temporal pattern was observed in the SAINTEX cohort, although the difference between admission CRP levels and 30-day hsCRP was not significant (Figure 1B).

3.3 | CRP at different time points in relation to acute cardiac injury

We assessed admission, peak and 1-month follow-up CRP levels in relation to markers of acute cardiac injury (Table 2). Admission CRP levels correlated weakly with EF in the acute phase, both in the MI cohort (coefficient -0.164 , $P = 0.094$) and the SAINTEX cohort (-0.323 , $P = 0.051$), although this correlation did not reach statistical significance. However, peak CRP levels were strongly associated with most markers of cardiac injury, such as ejection fraction (coefficient -0.4 , $P < 0.001$), peak high sensitivity Troponin T (coefficient 0.389 , $P < 0.001$), peak CK-MB (coefficient 0.378 , $P < 0.001$), and white blood cell count (coefficient 0.389 , $P < 0.001$) in the MI cohort. These findings were replicated in the 57 patients of the SAINTEX cohort. hsCRP levels at 1 month post-MI did not appear to be related anymore to the extent of acute cardiac injury.

TABLE 2 Association between C-reactive protein at three separate time points and markers of acute cardiac injury

	CRP admission		CRP peak		hsCRP day 30	
	Coefficient	P value	Coefficient	P value	Coefficient	P value
MI cohort (n = 131)						
ST-elevation	0.032	0.726	0.148	0.105	0.090	0.105
Anterior MI	0.018	0.837	-0.002	0.985	0.018	0.837
EF acute phase (%)	-0.164	0.094	-0.400	<0.001	0.012	0.908
Peak hsTnT (µg/L)	0.085	0.336	0.389	<0.001	0.040	0.657
Peak CK-MB (µg/L)	0.057	0.561	0.378	<0.001	-0.088	0.370
WBC count (10 ⁶ /L)	0.232	0.008	0.389	<0.001	0.058	0.516
Neutrophils (%)	0.243	0.006	0.320	<0.001	0.074	0.414
SAINTEX cohort (n = 57)						
ST-elevation	0.129	0.381	-0.047	0.729	-0.047	0.729
Anterior MI	0.004	0.980	0.035	0.812	-0.017	0.898
EF acute phase (%)	-0.323	0.051	-0.285	0.087	-0.199	0.196
Peak CK-MB (µg/L)	0.168	0.265	0.292	0.049	-0.046	0.741
WBC count (10 ⁶ /L)	0.035	0.814	0.268	0.066	0.047	0.748
Neutrophils (%)	-0.167	0.263	0.023	0.877	-0.068	0.646

Abbreviations: CK-MB, MB-creatin kinase; CRP, C-reactive protein; EF, ejection fraction; hs, high-sensitivity; TnT, Troponin T; WBC, white blood cell. (hs) CRP levels are log-transformed.

P values <0.05 are given in bold.

3.4 | CRP at different time points for the prediction of LV dysfunction at follow-up

We next investigated to what extent CRP levels at these three time points predicts left ventricular function at follow-up (Table 3). Peak CRP, but not CRP on admission or at 1 month, was significantly correlated with ejection fraction at follow-up in the MI cohort (coefficient

-0.245, $P = 0.012$). A similar correlation was observed in the SAINTEX cohort (coefficient -0.248, $P = 0.097$). Other identified predictors of LV function include the presence of ST-elevation (coefficient -0.222 for presence of ST-elevation, $P = 0.024$), peak CK-MB (coefficient -0.469, $P < 0.001$) or hs Troponin T levels (coefficient -0.512, $P < 0.001$), and the ejection fraction in the acute phase of MI (coefficient 0.595, $P < 0.001$).

TABLE 3 Univariable predictors of left ventricular function at follow-up

	MI cohort (n = 131)		SAINTEX cohort (n = 57)	
	Coefficient	P value	Coefficient	P value
Demographics				
Age	0.001	0.991	0.006	0.968
Sex (male)	0.024	0.806	0.025	0.856
Hypertension	0.008	0.930	0.021	0.879
Diabetes	-0.138	0.152	0.071	0.605
Current smoker	-0.061	0.525	-0.096	0.484
Hypercholesterolemia	-0.147	0.126	-0.150	0.276
Acute cardiac injury				
ST-elevation	-0.222	0.024	-0.123	0.369
Anterior MI	0.073	0.449	0.230	0.091
Acute EF (%)	0.595	<0.001	0.216	0.170
Peak hsTnT (µg/L)	-0.512	<0.001		
Peak CK-MB (µg/L, log)	-0.469	<0.001	-0.190	0.173
WBC count (10 ⁶ /L)	-0.450	<0.001	-0.069	0.645
Neutrophils (%)	-0.316	0.001	0.063	0.680
CRP levels				
CRP admission (mg/L, log)	-0.058	0.544	0.007	0.963
Peak CRP (mg/L, log)	-0.245	0.012	-0.248	0.097
hsCRP day 30 (mg/L, log)	-0.005	0.958	-0.002	0.991

Abbreviations: CK-MB, MB-creatin kinase; CRP, C-reactive protein; EF, ejection fraction; hs, high-sensitivity; MI, myocardial infarction; TnT, Troponin T; WBC, white blood cell.

P values <0.05 are given in bold.

We finally combined the patients from both cohorts to assess whether peak CRP is an independent predictor of left ventricular dysfunction at follow-up. In total, 18 patients reached this end point. In an univariable analysis, peak CRP significantly predicted left ventricular dysfunction at follow-up (OR 11.0, 3.1-39.5 per log CRP, $P < 0.001$). When adjusting for infarct size measured by CK-MB, peak CRP remained independently associated with LV dysfunction at follow-up (OR 5.1, 1.1-23.6, $P = 0.037$). Analysis of the ROC-curve identified an optimal cut-off value of 38.6 mg/L for peak CRP, with a sensitivity of 0.63 (0.35-0.85 95% CI) and specificity of 0.89 (0.83-0.94) (Figure 2A). Patients with peak CRP above 38.6 mg/L had a significantly higher risk of developing LV dysfunction (34.6% vs 4.0%, log-rank $P < 0.001$, Figure 2B).

4 | DISCUSSION

In this observational study, we examined the different roles of CRP measured in the acute phase of MI compared to levels at 1 month follow-up for the prediction of left ventricular function. Peak CRP during hospitalization with acute MI is associated with markers of acute cardiac injury and is an independent predictor of left ventricular dysfunction at follow-up. However, hsCRP 1 month post-MI as marker of ongoing inflammation appears not to be associated with the extent of acute cardiac injury

or ejection fraction at follow-up. These findings may be relevant for the timing of novel anti-inflammatory therapies in ischemic heart disease.

The observation that specifically peak levels of CRP are related to infarct size and left ventricular function at follow-up confirms findings from previous studies.^{2,3} Peak CRP may therefore be taken into account when gauging the risk of adverse outcome in patients with MI. Myocardial ischemia results in a well-orchestrated inflammatory response, including the release of damage associated molecular patterns by the ischemic myocardium, the recruitment of neutrophils and monocytes to the infarcted myocardium and induction of healing.¹ Limiting the extent of cardiac injury blunts the CRP response.¹³ An imbalanced or excessive inflammatory response may therefore correlate with clinical outcomes. Since CRP is produced by the liver as result of an upstream cascade, and depending on the magnitude of recruitment of cells to the myocardium, it may take up to 48 hours to reach peak levels.

Although the inflammatory and proliferative phase after MI may last up to several weeks, we were not able to show a correlation between hsCRP measured 1 month post-MI and left ventricular function further on.⁴ Nevertheless, hsCRP 1 month post-MI is a known predictor of recurrent ischemic events^{8,14} and cardiovascular death, including pump failure.¹⁵ It is also increased in patients with stable heart failure.^{16,17} These observations suggest that hsCRP measured 1 month post-MI might at least in part be driven by other pathophysiological mechanisms, rather than inflammation related to the infarct healing process itself. Alternatively, hsCRP may be not the correct marker to assess cardiac inflammation 1 month post-MI.

Since chronic low-grade inflammation relates to ischemic events, the inflammation caused by acute infarction may increase susceptibility to recurrent events.¹⁸ One study showed that patients with a large MI and consequently high inflammatory activation were at increased risk of recurrent events compared to patients with smaller MIs.¹⁹ The increased number of recurrent events were especially observed in the first 30 days post-MI and not thereafter, suggesting that the infarct size-induced inflammation may have subsided after 30 days.

Whether administering anti-inflammatory treatments 1 month post-MI would also interfere with the acute cardiac component of the ongoing inflammation as opposed to low-level chronic vascular inflammation, remains unknown. Nevertheless, this question is important in light of the results of the CANTOS trial.⁹ In a study in which the IL-1 receptor antagonist anakinra was administered to patients in the acute phase of MI, CRP levels were only temporarily reduced during study drug administration, returning to baseline levels after discontinuation.²⁰ Moreover, there was an excess of events in the anakinra group. Therefore, there clearly is a need to identify the optimal time frame for initiating anti-inflammatory treatments in both acute MI as well as stable coronary artery disease.

In this observational study, we have tried to tease out the respective roles of CRP measured during and after MI with respect to its relation with cardiac injury. Although patients were prospectively included, no causal relation can be derived from the associations we observed in our analyses. Although we did correct for infarct size when establishing the prognostic role of peak CRP, our study was not adequately powered to correct for other cardiovascular risk markers or drug therapies. We determined CRP at clinically relevant time points (during admission, at 1 month follow-up), but in-between CRP levels at 1 and 2 weeks post-MI could also be of interest to better gauge the complete course

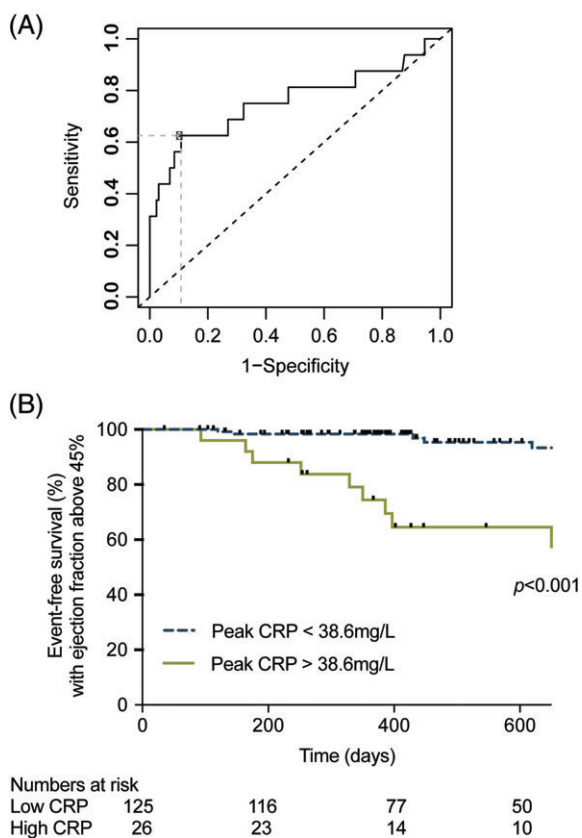


FIGURE 2 A, ROC-curve showing the sensitivity and specificity of different cut-off values of peak CRP for the prediction of LV dysfunction. The optimal cut-off value was calculated to be 38.6 mg/L. B, Patients with high peak CRP levels had a significantly higher risk to develop LV dysfunction compared to patients with low peak CRP levels. CRP, C-reactive protein; hsCRP high-sensitivity C-reactive protein; LV dysfunction, left ventricular dysfunction; MI, myocardial infarction; ROC, receiver operating characteristics

of CRP release. We also did not perform cardiac magnetic resonance (CMR) imaging to assess infarct size, but used peak troponin T or CK-MB as biochemical proxy for the extent of cardiac injury. Although peak troponin T is a validated marker of cardiac injury, CMR in both the acute phase as well as at follow-up can provide more detailed information on the extent of cardiac injury, remodeling, and fibrosis.¹¹

Finally, the replication cohort consisted of a smaller number of patients, resulting in lower statistical significance of the correlations. Although a larger patient cohort would have allowed to correct for more clinical variables, we believe that future studies should especially focus on more specific ways of assessing cardiac inflammation in the acute phase and at 1 month follow-up. CRP is indeed a generic downstream marker of inflammation, and therefore new inflammatory biomarkers to identify high-risk patients need to be developed. A tailored approach, for example, by using cytokine or gene profiling, might be able to improve the prediction of LV dysfunction on top of classical markers, and identify patients with potential benefit of anti-inflammatory treatment.^{21,22}

5 | CONCLUSIONS

In this study, hsCRP measured 1 month post-MI did not relate to the extent of acute cardiac injury and did not contribute to the prediction of LV dysfunction at follow-up. Conversely, we confirmed findings from previous studies that peak CRP relates to acute cardiac injury and is an independent predictor of LV dysfunction at follow-up.

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Conflict of interest

The authors declare no potential conflict of interests.

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