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Relation of inflammatory markers with myocardial and microvascular injury in patients with reperfused ST-elevation myocardial infarction

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Abstract

Background: In patients with acute ST-elevation myocardial infarction (STEMI), elevated concentrations of inflammatory markers are correlated with worse clinical outcome. The aim of this study was comprehensively to investigate the relationship of circulating markers of inflammation with myocardial and microvascular damage after STEMI.

Methods: In 111 consecutive STEMI patients, blood samples were obtained on admission and from day 1 to day 4 after primary percutaneous coronary intervention and analysed for high-sensitivity C-reactive protein (hs-CRP), white blood cell count and fibrinogen. Cardiac magnetic resonance imaging was performed within the first week and 4 months after primary percutaneous coronary intervention.

Results: Peak concentrations of hs-CRP (20.5 (9.6–44.4) mg/L), white blood cell count (12.4 (10.5–15.3) G/L) and fibrinogen (3640 (3150–4550) mg/L) showed significant correlations with both infarct size (r=0.31 to 0.41; P<0.01) and left ventricular ejection fraction (r=−0.29 to −0.39; P<0.01) assessed in the acute as well as chronic stage following STEMI. Furthermore, peak concentrations of these inflammatory markers were significantly higher in patients with microvascular obstruction compared to patients without microvascular obstruction ($P \leqslant 0.01$). C-statistics revealed that the prognostic values of all three biomarkers for the prediction of large chronic infarct size (>8% of left ventricular myocardial mass) were moderate without significant differences (area under the curve: hs-CRP 0.73 (95% confidence interval (CI) 0.63–0.82), white blood cell count 0.67 (95% CI 0.56–0.78) and fibrinogen 0.69 (95% CI 0.59–0.79); all P>0.12). Combination of inflammatory markers did not significantly increase the area under the curve (P>0.05).

Conclusion: In reperfused STEMI patients, increased levels of hs-CRP, white blood cell count and fibrinogen are associated with decreased left ventricular function and more pronounced myocardial damage at baseline and 4 months after infarction.

Keywords

ST-elevation myocardial infarction, magnetic resonance imaging, inflammatory markers, high-sensitivity C-reactive protein, white blood cell count, fibrinogen

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Introduction

Not only in the pathogenesis of atherosclerosis, but also in the acute setting of acute myocardial infarction and during the period of myocardial recovery following infarction, inflammation plays an important role.[1,2] Especially C-reactive protein (CRP) is the most extensively investigated inflammatory marker in patients with acute

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coronary syndrome (ACS) and was demonstrated to be a strong predictor of adverse outcome.[3] In addition, white blood cell count (WBCc) and fibrinogen were shown to be associated with worse clinical outcome in ACS patients.[4,5]

The severity of myocardial damage after ST-elevation myocardial infarction (STEMI) is strongly connected with short and long-term clinical outcome.[6] Indeed, there is increasing evidence that especially infarct size (IS) as well as microvascular obstruction (MVO) as determined by cardiac magnetic resonance (CMR) imaging provide strong prognostic information that is incremental to clinical risk factors and left ventricular ejection fraction (LVEF).[6] As such, CMR imaging is able to provide unique insights into the relation between circulating biomarkers of inflammation and prognostically relevant infarct characteristics after STEMI.[7]

However, these potential relations have not been sufficiently studied so far. Therefore, we aimed to evaluate comprehensively the association of three routine markers of inflammation (high sensitivity (hs)-CRP, WBCc and fibrinogen) with CMR-determined infarct characteristics after STEMI. Furthermore, we sought to assess their utility for the prediction of large infarct scar, left ventricular (LV) systolic dysfunction and remodelling 4 months after infarction and compared their prognostic value with the current gold-standard biomarker, high-sensitivity cardiac troponin T (hs-cTnT).

Methods

Study design and biochemical measurements

One hundred and eleven consecutive patients with first acute STEMI were included in this observational study. The redefined European Society of Cardiology/American College of Cardiology committee criteria were used for the diagnosis of STEMI,[8] and the following inclusion criteria were applied: (a) reperfusion with primary percutaneous coronary intervention (PPCI) within 12 hours after symptom onset; (b) no history of a previous myocardial infarction; (c) an estimated glomerular filtration rate >30 mL/min/1.73 m²; (d) Killip class <3; and (e) no contraindications to CMR examination. CMR scans were performed within the first week following PPCI and 4 months thereafter. Blood samples were obtained by peripheral venipuncture on admission immediately prior to PPCI and after study inclusion subsequently once daily up to day 4 following PPCI. For hs-CRP, WBCc and fibrinogen measurements, routine assays were used, as previously described.[9] For the assessment of hs-cTnT concentration, heparinised plasma samples were analysed by an enzyme immunoassay (hs-cTnT; E170, Roche Diagostics, Vienna, Austria). The analytical limit of detection and the 99th percentile upper reference limit were 5 ng/L and 14 ng/L, respectively, and the coefficient of variation was <10% at 13 ng/L.[10] The study was conducted in conformity with the Declaration of Helsinki and was approved by the local research ethics committee.

Cardiac magnetic resonance imaging

For CMR imaging, a 1.5 Tesla Magnetom AVANTO-scanner (Siemens, Erlangen, Germany) was used. The detailed description of the imaging protocol was previously published.[11] Short-axis cine images using breath-hold, retrospective ECG-triggered trueFISP bright-blood sequences were acquired to assess LV morphology and function.[11] Images were analysed by using standard software (ARGUS, Siemens, Erlangen, Germany).[11] LV adverse remodelling was defined as an increase of end-diastolic volume ⩾20%.[11] Impaired LV function was defined as LVEF <55%.[12] Late enhancement (LE) CMR images were acquired by using an ECG-triggered phase-sensitive inversion recovery sequence with consecutive short-axis slices.[12] The extent of LE was analysed quantitatively using a commercially available software tool (J-Vision vs. 3.3.16, TIANI Medgraph, Brunn am Gebirge, Austria) by defining 'hyperenhancement' as a threshold of +5 SD above the signal intensity of remote myocardium.[12] Large IS was defined as >8% of LV myocardial mass.[12] MVO was defined as a zone of persisting 'hypoenhancement' within the area of 'hyperenhancement'.[12]

Statistical analysis

Statistical analysis was performed using SPSS Statistics 22.0 (IBM, Armonk, NY, USA) and MedCalc version 15.8 (Ostend, Belgium). Continuous variables were expressed as mean ± standard deviation or as median with interquartile range. Normal distribution was assessed using the Kolmogorov–Smirnov test. Categorical variables were expressed as number and corresponding percentage. Correlations of continuous variables were calculated applying Pearson or Spearman test. Strengths of correlations were interpreted according to the classification provided by Statistics at Square One.[13] Fisher's r-to-z transformation was used to compare correlation coefficients. The Mann–Whitney U test was applied to appraise differences in continuous variables between two groups. The χ^2-test was used to compare categorical variables between groups. Differences in CMR parameters between baseline and follow-up were assessed using the Wilcoxon signed-rank test. C-statistic was used to determine the area under the curve (AUC). C-statistic results were compared by a non-parametric method published previously.[14] To determine independent predictors of large IS and MVO, multivariate logistic regression analysis was applied. A two-tailed P value of <0.05 was defined as statistically significant.

Results

Study population and CMR findings

One hundred and eleven STEMI patients, revascularised by PPCI with a median treatment delay of 206 (143–365) minutes, were included. A detailed overview on baseline clinical characteristics is provided in Table 1.

Table 1. Patient characteristics (*n*=111).

Characteristic	Mean/median/number
Age, years	57 (±10)
Female, *n* (%)	13 (12)
Body mass index, kg/m²	26 [25–28]
Hypertension, *n* (%)	71 (64)
Systolic blood pressure, mmHg	124 [112–143]
Diastolic blood pressure, mmHg	77 [70–90]
Family history for AMI, *n* (%)	32 (29)
Current smoker, *n* (%)	58 (52)
Hyperlipidaemia, *n* (%)	69 (62)
Diabetes mellitus, *n* (%)	10 (9)
Number of diseased vessels, *n* (%)	
1	60 (54)
2	37 (33)
3	14 (12)
Culprit lesion, *n* (%)	
RCA	53 (48)
LAD	45 (41)
LCX	13 (12)
Time from symptom onset to PPCI, min	206 [143–365]
TIMI flow pre-PPCI, *n* (%)	
0	68 (61)
1	18 (16)
2	24 (22)
3	1 (1)
TIMI flow post-PPCI, *n* (%)	
0	0 (0)
1	2 (2)
2	11 (10)
3	98 (88)
Admission hs-CRP, mg/L	2.1 [1.1–5.6]
Peak hs-CRP, mg/L	20.5 [9.6–44.4]
Admission WBCc, G/L	11.3 [8.9–14.0]
Peak WBCc, G/L	12.4 [10.5–15.3]
Admission fibrinogen, mg/L	3070 [2510–3500]
Peak fibrinogen, mg/L	3640 [3150–4550]
Admission hs-cTnT, ng/L	120 [21–1947]
Peak hs-cTnT, ng/L	5464 [2337–8574]
Concomitant medication, admission	
Antiplatelet therapy, *n* (%)	14 (13)
ACE inhibitors/ARBs, *n* (%)	16 (14)
β-blockers, *n* (%)	19 (17)
Statins, n (%)	18 (16)
Concomitant medication, discharge	
Antiplatelet therapy, *n* (%)	111 (100)
ACE inhibitors/ARBs, *n* (%)	98 (88)
β-blockers, *n* (%)	97 (87)
Statins, *n* (%)	110 (99)
Concomitant medication, follow-up	
Antiplatelet therapy, (%)	111 (100)
ACE inhibitors/ARBs, *n* (%)	96 (87)
β-blockers, *n* (%)	93 (84)
Statins, n (%)	107 (96)

AMI: acute myocardial infarction; RCA: right coronary artery; LAD: left anterior descending artery; LCX: left circumflex artery; PPCI: primary percutaneous coronary intervention; hs-CRP: high-sensitivity C-reactive protein; WBCc: white blood cell count; hs-cTnT: high-sensitivity cardiac troponin T; ARBs: angiotensin receptor blockers.

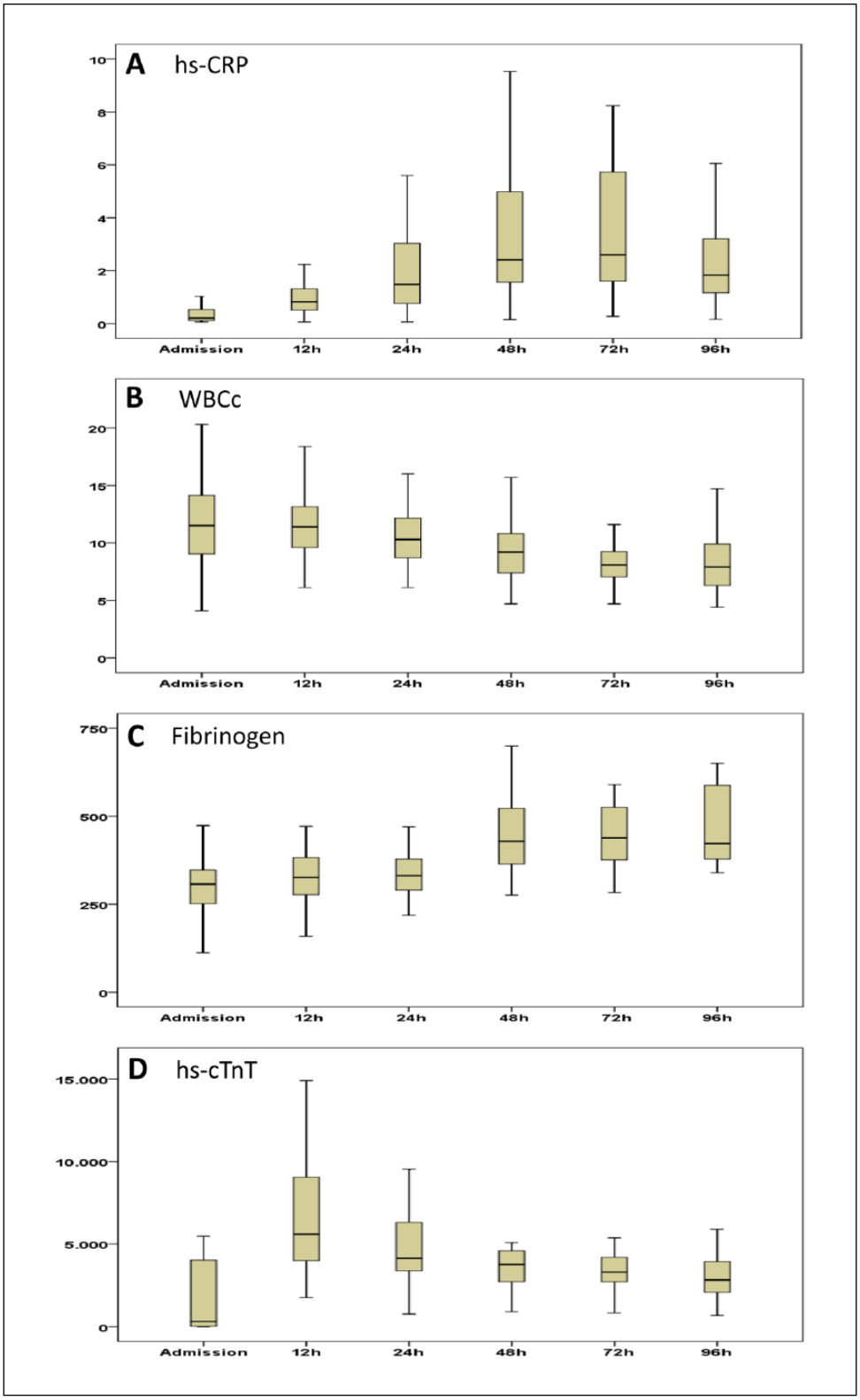

Figure 1. Release kinetic curves of (a) high-sensitivity C-reactive protein (hs-CRP) (mg/dL), (b) white blood cell count (WBCc) (G/L), (c) fibrinogen (mg/dL) and (d) high-sensitivity cardiac troponin T (hs-cTnT) (ng/L).

The release kinetic curves of the investigated biomarkers are displayed in Figure 1.

CMR scans were performed at a median of 2 (1–4) days as well as 124 (120–138) days after PPCI. CMR

Table 2. CMR parameters.

	Baseline	Follow-up	Difference	*P* value
LVEF,%	55 [49–61]	61 [54–66]	6 [0–10]	<0.001
IS,% of LVMM	16 [9–25]	11 [6–16]	6 [0–10]	<0.001
LVEDVI, mL/m²	74 [66–82]	79 [66–89]	3 [–4–10]	0.01
LVESVI, mL/m²	32 [26–41]	29 [23–38]	2 [–3–8]	<0.001
MVO, *n* (%)	59 (53%)	NA	NA	NA

CMR: cardiac magnetic resonance; LVEF: left ventricular ejection fraction; IS: infarct size; LVMM: left ventricular myocardial mass; LVEDVI: left ventricular end-diastolic volume index; LVESVI: left ventricular end-systolic volume index; MVO: microvascular obstruction; NA: not applicable.

Table 3. Correlations between biomarkers and CMR parameters.

	Peak hs-CRP	Peak WBCc	Peak fibrinogen	Peak hs-cTnT
LVEF (BL)	−0.32**	−0.35**	−0.30**	−0.56**
IS (BL)	0.36**	0.35**	0.36**	0.72**
LVEF (4FU)	−0.35**	−0.39**	−0.29**	−0.51**
IS (4FU)	0.41**	0.31**	0.34**	0.78**

**$P<0.01$.
CMR: cardiac magnetic resonance; hs-CRP: high-sensitivity C-reactive protein; WBCc: white blood cell count; hs-cTnT: high-sensitivity cardiac troponin T; BL: baseline; 4FU: 4 months follow-up; LVEF: left ventricular ejection fraction; IS: infarct size.

Table 4. Differences in biomarker concentrations in patients without versus with MVO.

	MVO–	MVO+	*P* value
Peak hs-CRP, mg/L	13.8 [7.1–23.7]	30.1 [16.4–53.1]	<0.001
Peak WBCc, G/L	11.5 [9.6–12.9]	12.9 [11.3–16.6]	0.01
Peak fibrinogen, mg/L	3410 [3020–3843]	3830 [3400–5090]	0.003
Peak hs-cTnT, ng/L	4050 [1156–6672]	6788 [4303–11161]	<0.001

MVO: microvascular obstruction; hs-CRP: high-sensitivity C-reactive protein; WBCc: white blood cell count; hs-cTnT: high-sensitivity cardiac troponin T.

parameters are listed in Table 2. Briefly, LVEF significantly increased from baseline to follow-up, whereas IS significantly decreased in the same period of time. Adverse remodelling occurred in 23%; MVO was present in 53% of our patient population.

Association of biomarkers with CMR findings

For admission levels of hs-CRP and fibrinogen, no significant correlation with CMR parameters was detected (all $P>0.05$); however, admission WBCc was weakly but significantly correlated to baseline as well as follow-up IS and LVEF (all $P<0.01$). All peak concentrations of inflammatory markers showed similar correlations with CMR parameters (all $P\geqslant0.40$, Table 3). Hs-cTnT displayed significantly higher correlations with baseline and follow-up IS ($P<0.001$) and baseline LVEF ($P<0.05$) as compared to the inflammatory biomarkers (Table 3). We also tested for potential determinants of increased peak hs-CRP levels (>10 mg/l)[15] besides necrosis; however, no baseline characteristic showed a significant association with elevated peak hs-CRP (all $P>0.11$).

Patients with MVO had significantly higher peak levels of all tested biomarkers compared to the group without MVO (Table 4). Furthermore, patients with LV adverse remodelling showed significantly higher peak concentrations of hs-CRP ($P=0.04$), WBCc ($P=0.03$) and hs-cTnT ($P<0.001$), whereas peak fibrinogen did not differ significantly ($P=0.07$).

Predictive values of biomarkers

The AUC values for the prediction of large IS ($n=65$, 59%), impaired LVEF ($n=31$, 30%) and LV remodelling 4 months after STEMI are listed in Table 5. Among the inflammatory markers, no significant differences in AUC values were detected (all $P>0.05$). For the prediction of large IS, the AUC of hs-cTnT was significantly higher compared to all inflammatory markers (all $P<0.001$). For LVEF <55%, hs-cTnT showed a significantly higher AUC than hs-CRP ($P=0.04$) and fibrinogen ($P=0.02$); however, not than WBCc ($P=0.07$). The values for the prediction of remodelling were comparable for all tested biomarkers (AUC differences: all $P>0.05$).

Table 5. Receiver operating characteristic curve analysis for the prediction of chronic CMR parameters.

	AUC	95% CI	Best cut-off value	Sensitivity	Specificity
IS >8%					
Peak hs-CRP	0.73	0.63–0.82	15.6 mg/L	74%	62%
Peak WBCc	0.67	0.56–0.78	11.7 G/L	71%	59%
Peak fibrinogen	0.69	0.59–0.79	3545 mg/L	69%	59%
Peak hs-cTnT	0.94	0.90–0.98	4050 ng/L	90%	82%
LVEF <55%					
Peak hs-CRP	0.69	0.58–0.80	21.9 mg/L	68%	64%
Peak WBCc	0.69	0.59–0.80	12.2 G/L	84%	58%
Peak fibrinogen	0.64	0.52–0.76	3700 mg/L	68%	63%
Peak hs-cTnT	0.82	0.73–0.90	5919 ng/L	87%	71%
LV remodelling					
Peak hs-CRP	0.64	0.52–0.76	21.9 mg/L	68%	62%
Peak WBCc	0.64	0.51–0.76	12.4 G/L	76%	56%
Peak fibrinogen	0.62	0.49–0.76	4515 mg/L	52%	81%
Peak hs-cTnT	0.75	0.64–0.85	5476 ng/L	80%	59%

AUC: area under the curve; IS: infarct size; hs-CRP: high-sensitivity C-reactive protein; WBCc: white blood cell count; hs-cTnT: high-sensitivity cardiac troponin T; LVEF: left ventricular ejection fraction.

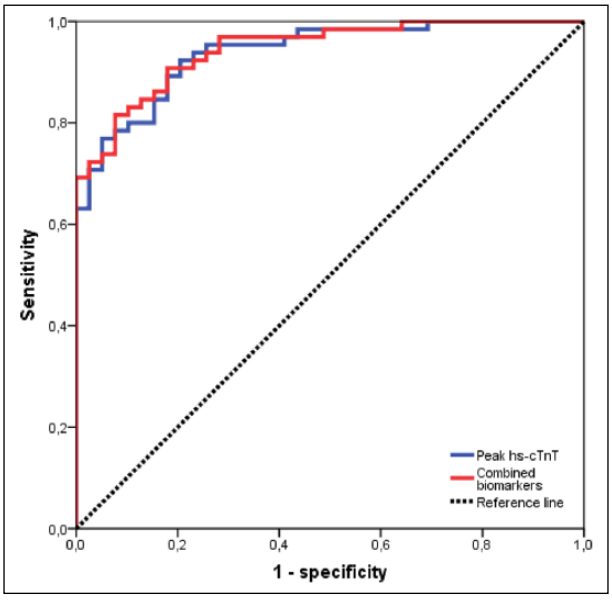

Figure 2. Receiver operating characteristic curves for the prediction of large infarct size (>8% of left ventricular myocardial mass; LVMM) 4 months after ST-elevation myocardial infarction (STEMI): combined biomarkers (peak high-sensitivity C-reactive protein (hs-CRP), white blood cell count (WBCc), fibrinogen and high-sensitivity cardiac troponin T (hs-cTnT)) versus peak hs-cTnT alone.

The combination of all four biomarkers (peak levels) did not reveal a higher AUC for the prediction of a large IS (AUC difference: 0.006, 95% confidence interval (CI) −0.007–0.017, P=0.37; Figure 2), LV dysfunction (0.015, 95% CI −0.023–0.054, P=0.45; Figure 3), or remodelling (0.020, 95% CI −0.035–0.074, P=0.48; Figure 4), as compared to peak hs-cTnT alone.

In multivariate analysis (Table 6), peak hs-cTnT independently predicted large final IS, whereas peak hs-CRP, WBCc and fibrinogen did not show significant correlations (all $P \geqslant 0.26$). For the prediction of MVO, peak hs-cTnT was the only independent correlate as well (inflammatory markers: all $P \geqslant 0.31$).

Discussion

In the present CMR study, we evaluated the relation between circulating inflammatory markers (hs-CRP, WBCc and fibrinogen) and main prognostic CMR parameters in reperfused STEMI. As far as we know, this is the first comprehensive CMR study investigating these three routine markers of inflammation together and in comparison with hs-cTnT in a relatively large STEMI cohort.

The major findings are as follows: (a) higher peak concentrations of hs-CRP, WBCc and fibrinogen are associated with a larger acute and chronic infarct size as well as with a lower LVEF at baseline and 4 months follow-up; (b) higher peak inflammatory markers were also found in patients with microvascular injury and in patients who developed adverse LV remodelling at follow-up; (c) inflammatory markers as well as hs-cTnT have the ability to predict large infarcts, LV dysfunction and remodelling 4 months after infarction; but (d) the combination of inflammatory markers with hs-cTnT did not lead to a higher predictive value as compared to hs-cTnT alone.

Inflammatory biomarkers and infarct characteristics

The association of inflammatory markers with the severity of myocardial injury is not completely clarified yet. Mather

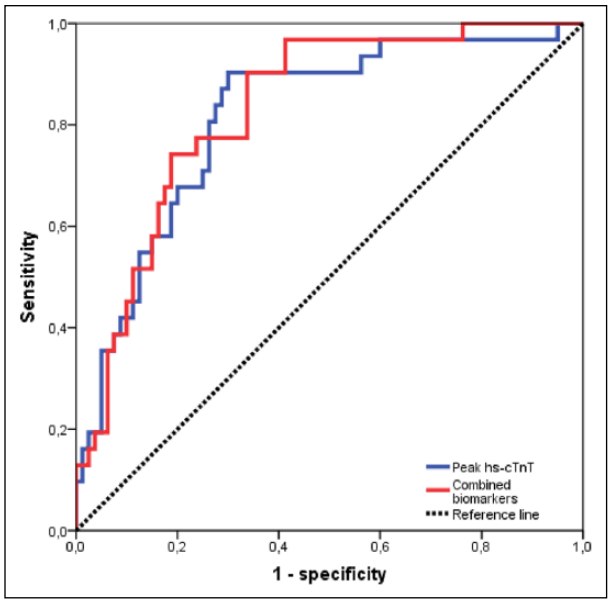

Figure 3. Receiver operating characteristic curves for the prediction of left ventricular dysfunction (left ventricular ejection fraction (LVEF) <55%) 4 months after ST-elevation myocardial infarction (STEMI): combined biomarkers (peak high-sensitivity C-reactive protein (hs-CRP), white blood cell count (WBCc), fibrinogen and high-sensitivity cardiac troponin T (hs-cTnT)) versus peak hs-cTnT alone.

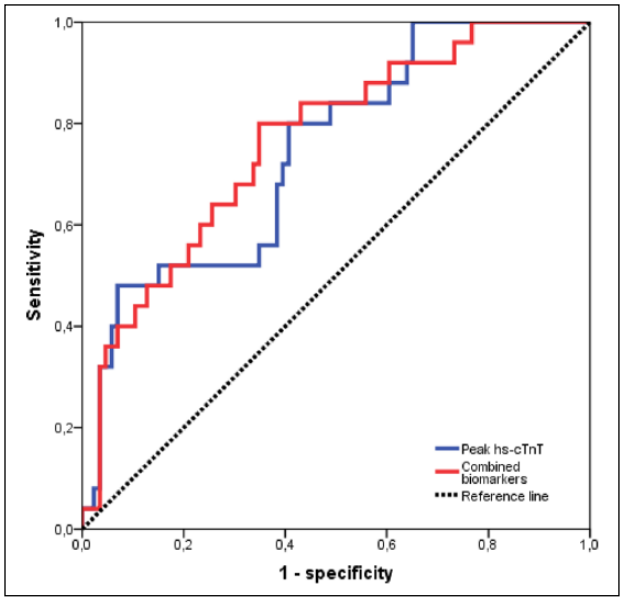

Figure 4. Receiver operating characteristic curves for the prediction of left ventricular adverse remodelling 4 months after ST-elevation myocardial infarction (STEMI): combined biomarkers (peak high-sensitivity C-reactive protein (hs-CRP), white blood cell count (WBCc), fibrinogen and high-sensitivity cardiac troponin T (hs-cTnT)) versus peak hs-cTnT alone.

et al. revealed a significant correlation of hs-CRP with IS;[16] however, hampered by a small study population. Confirming these data, our study showed that peak hs-CRP is significantly correlated to acute as well as chronic IS. Admission levels of hs-CRP did not correlate with IS, or with any other of the tested CMR parameters, most likely explainable by the delayed CRP release (Figure 1).[17] Recent studies have demonstrated that patients with high WBCc show larger acute IS after STEMI.[4,18] Furthermore, a significant relation between classic monocytes and chronic IS was reported;[19] however, the relevance of complete WBCc for the prediction of chronic IS has not been completely elucidated. To confirm and complement these results, our data depicted significant correlations of WBCc with acute and chronic IS. Worth mentioning, WBCc was the only inflammatory parameter to show weak but significant correlations also on admission, which might reflect the early release kinetics of neutrophiles.[17,18] Recently, fibrinogen at days 1, 4 and 7 after PPCI did not show significant correlations to final IS.[20] For single point measurements, we also could not find significant associations, but peak fibrinogen was weakly but significantly correlated to baseline and follow-up IS.

In accordance with prior findings,[21] our data confirmed that patients with MVO show significantly higher peak concentrations of hs-CRP. Moreover, MVO was significantly associated with WBCc, which was indicated previously.[19,22] Teunissen et al. could not detect a correlation between fibrinogen and microvascular injury;[20] however, we demonstrated a significant association between peak fibrinogen and MVO underlining the relevance of peak value assessments. In contrast, admission levels of all tested inflammatory markers did not show any significant relation with MVO, which is in agreement with previous findings.[23]

In STEMI patients, the role of inflammatory markers compared to hs-cTnT is largely unknown. In the study by Mather et al., troponin I was more strongly related to IS than hs-CRP.[16] In consonance with these results, we revealed a closer correlation of peak hs-cTnT with IS as compared to peak hs-CRP. Furthermore, we disclosed that peak WBCc and peak fibrinogen correlated less closely than peak hs-cTnT did with IS.

Inflammatory markers and LV function and remodelling

In STEMI patients, hs-CRP 2 days after reperfusion was shown to be correlated to baseline and follow-up LVEF.[16] However, CMR investigations on the relationship of WBCc with LVEF, especially chronic LVEF, are limited.[19] Significant correlations between chronic LVEF and fibrinogen were only stated for fibrinogen measurements at days 4 and 7 following STEMI.[20] Our data could confirm and extend these previous investigations by showing that peak hs-CRP, WBCc as well as fibrinogen levels were significantly correlated to acute and chronic LVEF.

Mather et al. found that hs-CRP concentrations on day 2 were more closely correlated with baseline and follow-up

Table 6. Multivariate analysis for the prediction of large chronic IS and MVO.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
IS >8%				
Peak hs-CRP	1.25 (1.04–1.50)	**0.02**	–	–
Peak WBCc	1.18 (1.04–1.34)	**0.01**	–	–
Peak fibrinogen	1.01 (1.00–1.01)	**0.001**	–	–
Peak hs-cTnT	1.00 (1.00–1.00)	**<0.001**	1.00 (1.00–1.00)	**<0.001**
MVO				
Peak hs-CRP	1.12 (1.01–1.25)	**0.03**	–	–
Peak WBCc	1.13 (1.02–1.26)	**0.02**	–	–
Peak fibrinogen	1.01 (1.00–1.01)	**0.01**	–	–
Peak hs-cTnT	1.00 (1.00–1.00)	**<0.001**	1.00 (1.00–1.00)	**0.004**

IS: infarct size; MVO: microvascular obstruction; hs-CRP: high-sensitivity C-reactive protein; WBCc: white blood cell count; hs-cTnT: high-sensitivity cardiac troponin T.

LVEF than troponin I.[16] However, our study in a larger population revealed a significantly closer correlation of hs-cTnT with baseline LVEF compared to all three inflammatory biomarkers, whereas the closer correlation of hs-cTnT with follow-up LVEF was not significant.

The association of routine markers of inflammation with LV remodelling after myocardial infarction is poorly investigated. Recently, Westman et al. emphasised that especially inflammation might contribute to maladaptive remodelling processes following infarction.[24] Although a relation between CRP levels and remodelling assessed by echocardiography was demonstrated,[25] there are no CMR investigations confirming these results. The present study revealed that patients with LV remodelling displayed significantly higher peak concentrations of hs-CRP and WBCc compared to those without remodelling, whereas peak fibrinogen did not differ significantly.

Predictive values of inflammatory markers

In a previous report, hs-CRP predicted IS, LVEF and remodelling 3 months after infarction.[16] Nevertheless, investigations assessing the predictive values of WBCc or fibrinogen for chronic CMR parameters are scarce[19,20] and especially their comparison with hs-cTnT has not been investigated so far. We could detect that hs-CRP, WBCc and fibrinogen predicted large infarcts, LV dysfunction and remodelling 4 months after STEMI, without significant differences. However, for the combination with hs-cTnT no higher AUC values were found compared to hs-cTnT alone. Moreover, in a multivariate model for the prediction of large final IS and MVO, all three markers of inflammation could not show correlations independently from hs-cTnT.

These results are of significant clinical relevance in the current era of high sensitivity assays. As our data disclosed that the additional assessment of inflammatory markers, including high-sensitivity measurements of CRP, did not yield an increased diagnostic benefit regarding myocardial injury as well as cardiac dysfunction and remodelling, the only assessment of hs-cTnT would be sufficient for an adequate evaluation of these prognostically relevant parameters in reperfused STEMI patients. However, this diagnostic superiority of hs-cTnT should not diminish the clinical impact of inflammation in the acute setting after infarction. Indeed, the significant association between inflammation and myocardial and microvascular damage was emphasised by our data. Accordingly, anti-inflammatory strategies might be potential therapeutic approaches to reduce IS and MVO. Very recently, investigations indicated a potential benefit of anti-inflammatory substances like colchicine[26] in patients with STEMI, which has to be further investigated in future studies.

Limitations

Although this is the largest CMR study comparing the relevance of different inflammatory markers with hs-cTnT, the sample size is still relatively small. Therefore, larger trials are needed to confirm these results. The study population represents a relatively selected cohort of stable STEMI patients in order to perform CMR scans. Therefore, critically ill patients are under-represented in this trial. The majority of the study population was male and only 9% had a diagnosis of diabetes mellitus prior to admission, thus further data about female patients and those with diabetes are required. Furthermore, the follow-up period of 4 months is relatively short; however, CMR parameters at baseline and 4 months after STEMI were shown to provide high prognostic significance.[6] Release kinetic curves showed that the concentrations of hs-CRP, WBCc and hs-cTnT started to decline within 4 days after PPCI; however, fibrinogen levels only showed stagnation. Accordingly, the actual peak value of fibrinogen could possibly occur after the analysed period of 4 days.

Nevertheless, a recent investigation by Teunissen et al. showed that fibrinogen levels have declined at day 7 after PPCI.[20]

Conclusion

In contemporary reperfused STEMI patients, peak levels of routine inflammatory markers were significantly correlated to myocardial injury and LV function in the acute setting after PPCI as well as 4 months thereafter. The inflammatory markers were able to predict large IS, LV dysfunction and remodelling 4 months after STEMI, but the addition of these biomarkers to hs-cTnT did not add any significant predictive value as compared to hs-cTnT alone.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

1. Frangogiannis NG, Smith CW and Entman ML. The inflammatory response in myocardial infarction. *Cardiovasc Res* 2002; 53: 31–47.
2. Metzler B, Mair J, Lercher A, et al. Mouse model of myocardial remodelling after ischemia: role of intercellular adhesion molecule-1. *Cardiovasc Res* 2001; 49: 399–407.
3. Sheikh AS, Yahya S, Sheikh NS, et al. C-reactive protein as a predictor of adverse outcome in patients with acute coronary syndrome. *Heart Views* 2012; 13: 7–12.
4. Chung S, Song YB, Hahn JY, et al. Impact of white blood cell count on myocardial salvage, infarct size, and clinical outcomes in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a magnetic resonance imaging study. *Internat J Cardiovasc Imaging* 2014; 30: 129–136.
5. Toss H, Lindahl B, Siegbahn A, et al. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *Circulation* 1997; 96: 4204–4210.
6. Reinstadler SJ, Thiele H and Eitel I. Risk stratification by cardiac magnetic resonance imaging after ST-elevation myocardial infarction. *Curr Opin Cardiol* 2015; 30: 681–689.
7. Klug G and Metzler B. Assessing myocardial recovery following ST-segment elevation myocardial infarction: short- and long-term perspectives using cardiovascular magnetic resonance. *Expert Rev Cardiovasc Ther* 2013; 11: 203–219.
8. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined – a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000; 36: 959–969.
9. Reinstadler SJ, Klug G, Feistritzer HJ, et al. Relation of plasma adiponectin levels and aortic stiffness after acute ST-segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2014; 3: 10–17.
10. Feistritzer HJ, Reinstadler SJ, Klug G, et al. N-terminal pro-B-type natriuretic peptide is associated with aortic stiffness in patients presenting with acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2015. DOI: 10.1177/2048872615610866. Epub ahead of print 9 October 2015.
11. Reinstadler SJ, Klug G, Feistritzer HJ, et al. Association of copeptin with myocardial infarct size and myocardial function after ST segment elevation myocardial infarction. *Heart* 2013; 99: 1525–1529.
12. Reinstadler SJ, Feistritzer HJ, Klug G, et al. High-sensitivity troponin T for prediction of left ventricular function and infarct size one year following ST-elevation myocardial infarction. *Int J Cardiol* 2015; 202: 188–193.
13. Swinscow TDV. *Statistics at Square One*, 9th edn. London: BMJ Publishing Group, 1997.
14. DeLong ER, DeLong DM and Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44: 837–845.
15. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; 107: 499–511.
16. Mather AN, Fairbairn TA, Artis NJ, et al. 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.
17. Liebetrau C, Hoffmann J, Dorr O, et al. Release kinetics of inflammatory biomarkers in a clinical model of acute myocardial infarction. *Circ Res* 2015; 116: 867–875.
18. Husser O, Bodi V, Sanchis J, et al. White blood cell subtypes after STEMI: temporal evolution, association with cardiovascular magnetic resonance – derived infarct size and impact on outcome. *Inflammation* 2011; 34: 73–84.
19. van der Laan AM, Hirsch A, Robbers LF, et al. A proinflammatory monocyte response is associated with myocardial injury and impaired functional outcome in patients with ST-segment elevation myocardial infarction: monocytes and myocardial infarction. *Am Heart J* 2012; 163: 57–65e2.
20. Teunissen PF, Tijssen R, van Montfoort ML, et al. Kinetics of coagulation in ST-elevation myocardial infarction following successful primary percutaneous coronary intervention. *Thromb Res* 2016; 137: 64–71.
21. 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.
22. Carrick D, Haig C, Ahmed N, et al. Myocardial hemorrhage after acute reperfused ST-segment-elevation myocardial infarction: relation to microvascular obstruction and prognostic significance. *Circ Cardiovasc Imaging* 2016; 9: e004148.

23. Niccoli G, Lanza GA, Spaziani C, et al. Baseline systemic inflammatory status and no-reflow phenomenon after percutaneous coronary angioplasty for acute myocardial infarction. *Int J Cardiol* 2007; 117: 306–311.
24. Westman PC, Lipinski MJ, Luger D, et al. Inflammation as a driver of adverse left ventricular remodeling after acute myocardial infarction. *J Am Coll Cardiol* 2016; 67: 2050–2060.
25. Swiatkiewicz I, Kozinski M, Magielski P, et al. Value of C-reactive protein in predicting left ventricular remodelling in patients with a first ST-segment elevation myocardial infarction. *Mediators Inflamm* 2012; 2012: 250867.
26. Deftereos S, Giannopoulos G, Angelidis C, et al. Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. *Circulation* 2015; 132: 1395–1403.