

C-reactive protein velocity predicts microvascular pathology after acute ST-elevation myocardial infarction

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ABSTRACT

Background: The role of C-reactive protein velocity (CRPv) as an early and sensitive marker of an excessive inflammatory response in the setting of acute ST-elevation myocardial infarction (STEMI) is only poorly understood. The aim of this study was to investigate, in patients with STEMI treated with primary percutaneous coronary intervention (PCI), the association of CRPv with microvascular infarct pathology.

Methods and results: This prospective cohort study included a total of 316 patients with STEMI undergoing PCI. CRPv was defined as the difference between CRP 24 ± 8 h and CRP at hospital admission, divided by the time (in h) that have passed during the two examinations. The association of biomarker levels with cardiac magnetic resonance (CMR)-determined microvascular obstruction (MVO) was evaluated. CMR was performed at a median of 3 [interquartile range 2–4] days after PCI. After adjustment for cardiac troponin T (cTnT), anterior infarction and TIMI flow pre and post-PCI, CRPv (odds ratio 2.70, 95% confidence interval (CI) 1.54–4.73; $p = 0.001$) remained significantly associated with the occurrence of MVO. CRPv (area under the curve [AUC] 0.76, 95% CI 0.71–0.81; $p < 0.001$) was a better predictor for MVO compared to 24 h CRP (AUC difference: 0.03, $p = 0.002$). The addition of CRPv to peak cTnT resulted in a higher AUC for MVO prediction than peak cTnT alone (AUC 0.86, 95% CI 0.82–0.90; $p < 0.001$ vs. AUC 0.84, 95% CI 0.79–0.88; $p < 0.001$. AUC difference: 0.02, $p = 0.042$).

Conclusions: In patients with STEMI treated with primary PCI, CRPv was associated with microvascular infarct pathology with a predictive value incremental to cTnT, suggesting CRPv as an early and sensitive biomarker for more severe infarct pathology and outcome.

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1. Introduction

In the context of the contemporary management of ST-elevation myocardial infarction (STEMI), microvascular obstruction (MVO) occurs in approximately 50% of patients treated with primary percutaneous coronary intervention (PCI) [1]. MVO is a marker of more severe outcome as it is strongly associated with subsequent adverse left ventricular (LV) remodeling and recurrent cardiovascular events including mortality [2].

The use of C-reactive protein (CRP) as a marker for adverse events has been suggested in both primary and secondary prevention

settings. In patients with acute STEMI, the acute phase CRP response begins about 6 h after ischemic symptom onset and reaches its maximum at day 2–3 thereafter [3,4]. CRP elevation is directly related to a greater extent of myocardial tissue damage [3,5,6] with subsequent major adverse cardiac events (MACE) [7–9]. Recently, C-reactive protein velocity (CRPv) has been considered as a very early and more sensitive risk marker compared to single time point measurements [10]. However, the exact role and comparative prognostic value of CRP level change over time versus single time point measurements is still largely unclear. In particular, the association with MVO, a major determinant of adverse outcome after STEMI [11,12] has not been comprehensively investigated so far. We therefore investigated the association of CRPv with MVO as assessed by cardiac magnetic resonance (CMR) imaging among patients with acute STEMI who were treated with primary PCI.

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2. Methods

2.1. Study design, clinical assessments and endpoint definitions

For this prospective cohort study, patients enrolled in the “Magnetic Resonance Imaging In Acute ST-Elevation Myocardial Infarction” (MARINA-STEMI) trial (NCT04113356) between 2011 and 2019 were evaluated for inclusion in the final analysis. For the current analysis, only patients meeting the following criteria were eligible: first STEMI according to the European Society of Cardiology/American College of Cardiology committee criteria [13], revascularization by primary PCI within 12 h after onset of ischemic signs or symptoms and Killip class <3 at time of CMR imaging. Exclusion criteria were defined as the inability or unwillingness to sign written informed consent, an age < 18 years, any history of a previous myocardial infarction or coronary intervention, high-sensitivity (hs) CRP >15 mg/l at time of hospital admission, fever (temperature > 38 °C) or experience of an acute infection with fever within 14 days prior to study inclusion, chronic inflammatory disease, an estimated glomerular filtration rate < 30 ml/min per 1.73 m² and any other contraindication to CMR examination (pacemaker, severe claustrophobia, orbital foreign body, cerebral aneurysm clip, or known or suggested contrast agent allergy to gadolinium).

Biochemical measurements of hs-cardiac troponin T (cTnT) and hs-CRP were performed as described previously [14]. Briefly, measurements of CRP were conducted on the cobas® 8000 modular analyzer (Roche Diagnostics®) and concentrations of cTnT were determined applying a validated enzyme immunoassay (hs-cTnT; E170, Roche Diagnostics®). CRP and cTnT values were measured at hospital admission, 6 ± 2 h, 12 ± 4 h, 24 ± 8 h and then daily until day 4 after PCI or discharge [15]. CRPv was defined as the difference between CRP 24 ± 8 h and CRP at hospital admission, divided by the time (in h) elapsed during the two examinations [10].

The primary objective of the present study was the association between CRPv and MVO as determined by CMR imaging. The secondary clinical endpoint was the occurrence of MACE defined as composite of all-cause death, myocardial re-infarction, and new congestive heart failure [16]. Re-infarction was defined according to the redefined European Society of Cardiology/American College of Cardiology committee criteria [13] and new congestive heart failure was determined as first episode of cardiac decompensation requiring intravenous diuretic therapy with or without hospital re-admission [16]. Telephone follow-ups were conducted by blinded and trained study personnel according to a standardized questionnaire at 4 months, 12 months and every 12 months thereafter to assess the occurrence of MACE after STEMI. All declared endpoints were checked afterwards by reviewing electronic medical records.

Prior to study inclusion, written informed consent was given by all participants. The study was designed and conducted in compliance with the Declaration of Helsinki and received approval by the research ethics committee of the Medical University of Innsbruck.

2.2. Cardiac magnetic resonance imaging

All CMR scans were conducted on a 1.5 Tesla Magnetom AVANTO-scanner (Siemens Healthineers AG) within the first week after treatment with primary PCI. The standardized imaging protocol of our research group was published in detail previously [17]. Briefly, LV volumes and function were assessed on short-axis (10–12 slices) cine images using breath-hold, retrospective electrocardiogram (ECG) triggered trueFISP bright-blood sequences. For postprocessing, standard software (ARGUS; Siemens) was applied. ECG-triggered, phase-sensitive inversion recovery sequences were used to obtain late gadolinium enhancement (LGE) images 15–20 min after application of a 0.2 mmol/kg bolus of contrast agent (Gadovist®, Bayer, Leverkusen, Germany). For quantification of infarct size (IS), a PACS workstation (IMPAX®, Agfa HealthCare, Bonn, Germany) was used, whereas

“hyperenhancement” was defined as +5 standard deviations above the signal intensity of remote LV myocardium [18,19]. IS was expressed as percentage of total LV myocardial mass (LVMM). MVO was defined as persisting area of “hypo-enhancement” within the hyperenhanced territory and was also reported as percentage of LVMM [16]. Regions of MVO were included in aggregate IS.

Incomplete protocol was defined as premature termination of the investigation due to patient, medical or technical concerns.

2.3. Statistical analyses

Continuous data are expressed as median with interquartile range (IQR) and categorical variables are presented as numbers with corresponding percentages. Differences in continuous and categorical variables between two groups were tested by Mann–Whitney *U* test and Chi-square test, respectively. Spearman's rank test was used to assess correlations between continuous variables. Z-scores were calculated to present odds ratios (OR) per 1 standard deviation increase. For multivariable testing, binary logistic regression analysis was used to reveal independent predictors of MVO. Parameters showing significant associations (*p* < 0.05) with MVO in univariable analysis were included into the multivariable model (Table 2: CRPv, anterior infarction, peak cTnT, thrombolysis in myocardial infarction (TIMI) flow pre and post PCI. Supplementary Table 2: CRPv, anterior infarction, peak cTnT, TIMI flow pre and post PCI, glycoprotein IIb/IIIa inhibitors). Receiver operating characteristic (ROC) curve analysis was applied to evaluate area under the curve (AUC) for the prediction of MVO. ROC-curves were compared according to DeLong et al. [20]. Following Rice and Harris, AUC values were categorized as negligible (≤0.55), small (0.56–0.63), moderate (0.64–0.70) and strong (≥0.71) [21]. In an explorative analysis, we performed Cox regression analysis for the prediction of MACE. MACE-free survival was estimated and depicted by the Kaplan–Meier method (best cut-off according to median CRPv), and differences were assessed by the log-rank test.

All tests were 2-tailed and the significance level was set at 0.05. SPSS Statistics 26.0 (IBM, Armonk, NY, USA) and MedCalc v19.0.7 (Ostend, Belgium) were used for statistical analyses.

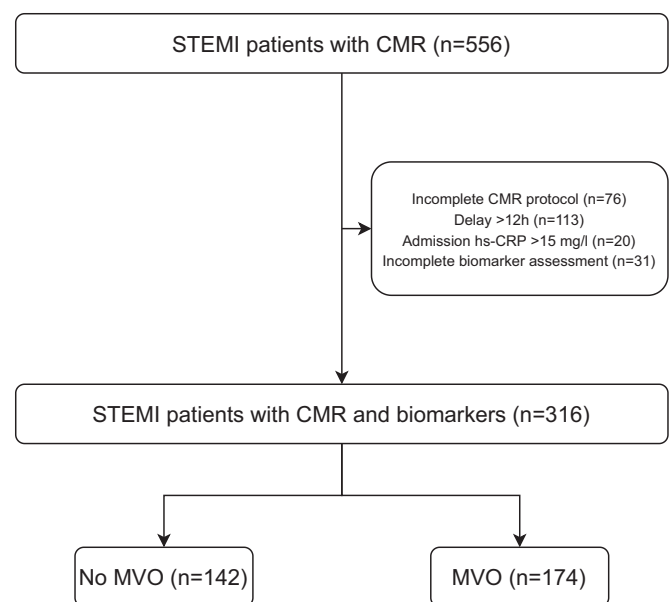


Fig. 1. Flow chart of the study cohort.

CMR = cardiac magnetic resonance, CRP = C-reactive protein, hs = high-sensitivity, MVO = microvascular obstruction, STEMI = ST-segment elevation myocardial infarction.

Table 1
Baseline patient characteristics.

| | Total population (n = 316) | No MVO (n = 142, 45%) | MVO (n = 174, 55%) | p-value |
|------------------------------------|-------------------------------|--------------------------|-----------------------|------------------|
| Age, years | 57[51–66] | 57[51–65] | 57[51–66] | 0.911 |
| Female, n (%) | 58(18) | 30(21) | 28(16) | 0.250 |
| Body mass index, kg/m ² | 26.1[24.6–28.7] | 26.2[24.4–28.7] | 26.0[24.6–29.1] | 0.992 |
| Current smoker, n (%) | 181(57) | 88(62) | 93(53) | 0.128 |
| Hyperlipidemia, n (%) | 174(55) | 79(56) | 95(55) | 0.854 |
| Diabetes mellitus, n (%) | 31(10) | 12(9) | 19(11) | 0.463 |
| Family history, n (%) | 120(38) | 55(39) | 65(37) | 0.517 |
| Hypertension, n (%) | 142(45) | 57(40) | 85(49) | 0.122 |
| Systolic blood pressure, mmHg | 137[115–154] | 140[118–159] | 132[114–150] | 0.054 |
| Diastolic blood pressure, mmHg | 82[73–96] | 82[73–97] | 82[72–95] | 0.629 |
| Heart rate, bpm | 72[63–85] | 71[63–84] | 74[63–86] | 0.397 |
| Total ischemia time, min | 176[120–259] | 171[122–258] | 183[120–262] | 0.687 |
| Culprit lesion, n (%) | | | | <0.001 |
| RCA | 127(40) | 76(54) | 51(29) | |
| LAD | 144(46) | 47(33) | 97(56) | |
| LCX | 42(13) | 17(12) | 25(14) | |
| RI | 3(1) | 2(1) | 1(1) | |
| Anterior infarction, n (%) | 147(47) | 50(35) | 97(56) | <0.001 |
| Number of affected vessels, n (%) | | | | 0.768 |
| 1 | 192(61) | 86(61) | 106(61) | |
| 2 | 89(28) | 42(30) | 47(27) | |
| 3 | 35(11) | 14(10) | 21(12) | |
| TIMI flow pre-PCI, n (%) | | | | <0.001 |
| 0 | 192(61) | 63(44) | 129(74) | |
| 1 | 42(13) | 21(15) | 21(12) | |
| 2 | 59(19) | 42(30) | 17(10) | |
| 3 | 23(7) | 16(11) | 7(4) | |
| TIMI flow post-PCI, n (%) | | | | 0.017 |
| 0 | 2(1) | 0(0) | 2(1) | |
| 1 | 5(1) | 1(1) | 4(2) | |
| 2 | 28(9) | 6(4) | 22(13) | |
| 3 | 281(89) | 135(95) | 146(84) | |
| Thrombus aspiration, n (%) | 7(2) | 2(1) | 5(3) | 0.379 |
| CRP, mg/l | | | | |
| Admission | 2.2[1.0–4.3] | 2.1[1.1–3.9] | 2.3[1.0–4.5] | 0.803 |
| 24 h | 13.0[8.0–21.0] | 10.0[6.3–14.7] | 18.2[9.6–30.4] | <0.001 |
| Peak | 22.6[13.1–45.6] | 15.8[9.4–22.7] | 38.4[19.9–66.6] | <0.001 |
| Admission to 24 h CRP, h | 22[20–25] | 22[19–25] | 22[20–26] | 0.527 |
| Admission to peak CRP, h | 47[36–60] | 43[29–55] | 48[42–62] | 0.001 |
| CRPv (admission to 24 h), mg/l/h | 0.42[0.24–0.83] | 0.30[0.15–0.46] | 0.67[0.34–1.14] | <0.001 |
| cTnT, ng/l | | | | |
| Admission | 113[27–699] | 64[20–223] | 206[35–1925] | <0.001 |
| 24 h | 3231[1541–5453] | 1633[690–3076] | 4774[3172–6804] | <0.001 |
| Peak | 4815[2359–8539] | 2493[1133–4498] | 6672[4661–11,345] | <0.001 |
| Admission to peak cTnT, h | 11[7–16] | 13[8–18] | 9[6–13] | <0.001 |

CRPv = C-reactive protein velocity, CRP = C-reactive protein, cTnT = cardiac troponin T, LAD = left anterior descending artery, LCX = left circumflex artery, LVEF = left ventricular ejection fraction, MVO = microvascular obstruction, PCI = percutaneous coronary intervention, RCA = right coronary artery, RI = ramus intermedius, TIMI = thrombolysis in myocardial infarction.

3. Results

3.1. Baseline patient characteristics

Three hundred and sixteen patients were included in final analysis. A study flow chart is shown in Fig. 1. CMR was performed at a median of 3 [IQR 2–4] days after PCI for STEMI. MVO was identified in 174 patients (55%). Table 1 presents baseline characteristics of the overall cohort ($n = 316$) as well as separately for patients with ($n = 174$, 55%) and without MVO ($n = 142$, 45%). Median admission CRP, 24 h CRP and peak CRP was 2.2 [IQR 1.0–4.3], 13.0 [IQR 8.0–21.0] and 22.6 [IQR 13.1–45.6] mg/l, respectively. CRPv was in median 0.42 [IQR 0.24–0.83] mg/l/h and significantly associated with MVO ($p < 0.001$) (Fig. 2). Except for admission CRP, concentrations of 24 h CRP, peak CRP, admission cTnT, 24 h cTnT and peak cTnT were significantly associated with MVO (all $p < 0.001$). CRPv significantly correlated with IS ($r = 0.497$, $p < 0.001$) and LVEF ($r = -0.378$, $p < 0.001$). Supplementary Table 1 displays anti-periprocedural anti-thrombotic therapy and medication at hospital discharge.

3.2. Predictors of microvascular obstruction

After multivariable analysis, CRPv (OR 2.70, 95% confidence interval (CI) 1.54–4.73; $p = 0.001$) and peak cTnT (OR 6.36, 95% CI 3.40–11.88; $p < 0.001$) emerged as independent predictors of MVO (Table 2). After adjustment for glycoprotein IIb/IIIa inhibitors in addition to parameters of Table 2, CRPv (OR 2.69, 95% CI 1.54–4.71; $p = 0.001$) remained a significant predictor of MVO (Supplementary Table 2). According to ROC analysis, 24 h CRP (AUC 0.73, 95% CI 0.67–0.77; $p < 0.001$), CRPv (AUC 0.76, 95% CI 0.71–0.81; $p < 0.001$) (Fig. 3A), peak CRP (AUC 0.78, 95% CI 0.74–0.83; $p < 0.001$) and peak cTnT (AUC 0.84, 95% CI 0.79–0.88; $p < 0.001$) strongly predicted MVO. The combination of peak cTnT and CRPv (AUC 0.86, 95% CI 0.82–0.90; $p < 0.001$, AUC difference: 0.02, $p = 0.042$) resulted in a higher AUC than peak cTnT alone (Fig. 3B). Furthermore, the combined predictive value of peak cTnT and peak CRP (AUC 0.87, 95% CI 0.83–0.91, $p < 0.001$, AUC difference: 0.01, $p = 0.149$) was not higher than the combination of peak cTnT and CRPv (Table 3). According to ROC analysis, the best cut-off value of CRPv in predicting MVO was >0.67 mg/l/h.

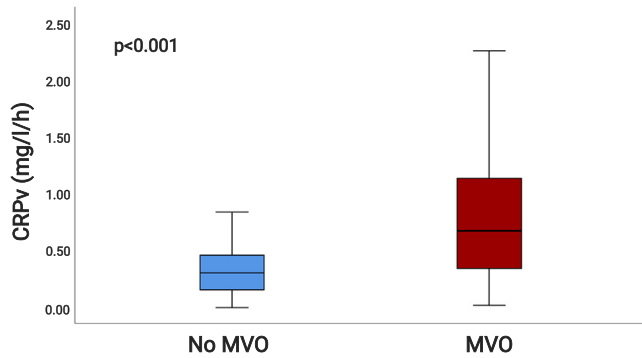


Fig. 2. Boxplot showing the relation between MVO and CRPv. CRPv = C-reactive protein velocity, MVO = microvascular obstruction.

Table 2
Binary logistic regression analysis for the prediction of MVO.

| | Univariable | | Multivariable | |
|---------------------|-------------------|------------------|------------------|------------------|
| | OR (95%CI) | p-value | OR (95%CI) | p-value |
| CRPv | 6.09(3.30–11.23) | <0.001 | 2.70(1.54–4.73) | 0.001 |
| Peak cTnT | 10.62(5.83–19.37) | <0.001 | 6.36(3.40–11.88) | <0.001 |
| Anterior infarction | 1.52(1.21–1.91) | <0.001 | 1.10(0.81–1.49) | 0.531 |
| TIMI flow pre-PCI | 0.51(0.40–0.65) | <0.001 | 0.77(0.57–1.04) | 0.093 |
| TIMI flow post-PCI | 0.63(0.46–0.87) | 0.005 | 0.80(0.56–1.16) | 0.243 |

CI = confidence interval, CRPv = C-reactive protein velocity, cTnT = cardiac troponin T, MVO = microvascular obstruction, OR = odds ratio, PCI = percutaneous coronary intervention. TIMI = thrombolysis in myocardial infarction. OR are presented per 1 standard deviation increase.

3.3. Clinical outcome

During a median follow-up time of 13 [IQR 6–25] months, 22 patients (7%) experienced a MACE (8 deaths, 8 re-infarctions and 6 heart failure events). Follow-up data was available in 311 patients (5 patients

were lost to follow-up, 1.6%). In an explorative analysis, CRPv above median (≥ 0.42 mg/l/h) was associated with adverse outcome (HR: 4.31, 95% CI 1.46–12.75; $p = 0.008$) and a lower MACE-free survival ($p = 0.004$) (Fig. 4).

4. Discussion

This study for the first time evaluated the association of CRPv with microvascular injury as assessed by CMR among patients with STEMI treated with primary PCI. The main findings of the present study were that (a) higher CRPv values were independently associated with more severe microvascular infarct pathology as defined by the presence of MVO; (b) CRPv showed a superior predictive validity compared to 24 h CRP and was comparable to peak CRP (in median at 2 days); (c) the addition of CRPv to peak cTnT resulted in a higher predictive value for MVO compared to peak cTnT alone; and (d) CRPv above median was associated with a higher rate of future cardiovascular events. Accordingly, these data add to the knowledge base of previous data by highlighting the potential value of CRPv as an early and sensitive biomarker for more severe microvascular tissue injury. These results indicate that CRPv, in addition to cardiac troponin, may play a role in early risk assessment after primary PCI for acute STEMI.

Imaging-driven strategies for early risk stratification after STEMI have more and more moved into focus [22]. CMR imaging is unique in its ability to characterize myocardial tissue in-vivo and has emerged as the most reliable imaging modality to depict microvascular injury and is therefore increasing more used to define surrogate endpoints in clinical trials [23]. MVO as determined by LGE CMR is suggested as strong prognosticator of adverse clinical outcome after acute STEMI [11,24]. In the present study, MVO occurred in 55% of patients which is in line with previous studies investigating acute STEMI patients treated with PCI [11]. However, CMR imaging is still rarely available and currently not integrated in clinical routine measurements. Therefore, the implementation of clinical available routine markers for the prediction of MVO is desirable.

Growing evidence indicates that CRP is not only a marker of inflammation and cardiovascular risk, but also a mechanistic mediator of

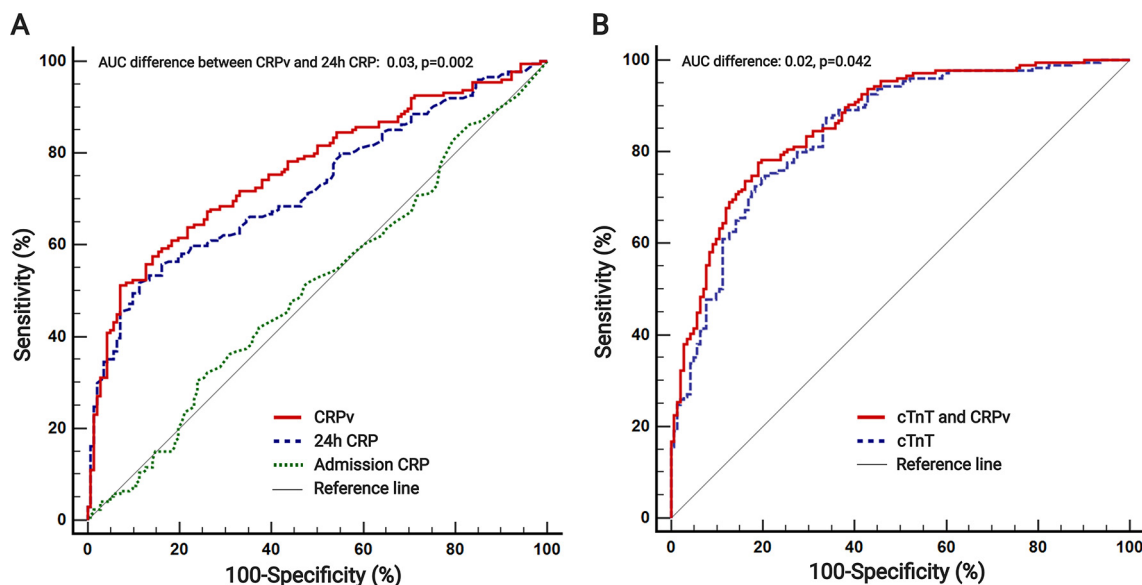


Fig. 3. ROC analysis for the prediction of MVO.

A. Admission CRP failed to predict MVO (AUC 0.51, 95% CI 0.44–0.57, $p = 0.803$), whereas CRPv was a better predictor of MVO than 24 h CRP (AUC 0.76, 95% CI 0.71–0.81, $p < 0.001$ vs. AUC 0.73, 95% CI 0.67–0.77, $p < 0.001$. AUC difference: 0.03, $p = 0.002$).
B. The combination of peak cTnT and CRPv revealed a significantly higher AUC than peak cTnT alone (AUC 0.86, 95% CI 0.82–0.90; $p < 0.001$ vs. AUC 0.84, 95% CI 0.79–0.88; $p < 0.001$. AUC difference: 0.02, $p = 0.042$).

AUC = area under the curve, CI = confidence interval, CRP = C-reactive protein, CRPv = C-reactive protein velocity, cTnT = cardiac troponin T, MVO = microvascular obstruction, ROC = receiver operating characteristic.

Table 3
C-statistics for the prediction of MVO.

| Variables | AUC | 95% CI | p-value | AUC increment | ROC comparison |
|----------------------|------|-----------|------------------|---------------|------------------|
| Admission CRP | 0.51 | 0.44–0.57 | 0.803 | – | – |
| 24 h CRP | 0.73 | 0.67–0.77 | <0.001 | 0.22 | <0.001 |
| CRPv | 0.76 | 0.71–0.81 | <0.001 | 0.03 | 0.002 |
| Peak CRP | 0.78 | 0.74–0.83 | <0.001 | 0.02 | 0.244 |
| Peak cTnT | 0.84 | 0.79–0.88 | <0.001 | 0.06 | 0.052 |
| Peak cTnT + CRPv | 0.86 | 0.82–0.90 | <0.001 | 0.02 | 0.042 |
| Peak cTnT + peak CRP | 0.87 | 0.83–0.91 | <0.001 | 0.01 | 0.149 |

AUC = area under the curve, CI = confidence interval, CRP=C-reactive protein, cTnT = cardiac troponin T, ROC = receiver operating characteristic.

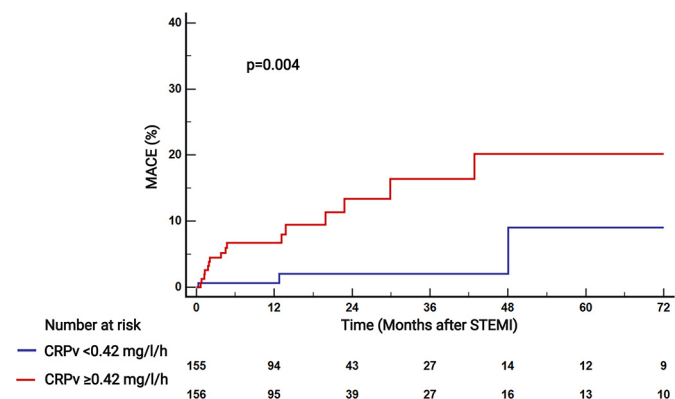


Fig. 4. CRPv and clinical outcome.
Kaplan-Meier curve displaying the MACE-free survival in relation to median CRPv.
CRPv = C-reactive protein velocity, MACE = major adverse cardiac events.

myocardial damage after STEMI [6,25–28]. Indeed, experimental and clinical studies suggested that CRP has pro-necrotic effects and is deposited in infarcted regions of the myocardium [26,29]. In the setting of acute myocardial infarction, inflammation and thrombosis seem to be closely related [30]. Actually, CRP may play a role as a local pro-inflammatory mediator during the acute phase of myocardial infarction by activating complement which can directly stimulate the coagulation cascade [31]. In addition, CRP alters the fibrinolytic balance of endothelial cells and therefore promotes intravascular fibrin formation [32]. These complex and only partially understood interactions with platelets, the blood coagulation and the fibrinolytic system may further explain the association of CRP and MVO after STEMI. On the basis of these findings, we assume that inflammation as measured by CRP may serve as a mechanistic link by causing progressive myocardial and endothelial injury as well as reduced repair within the infarcted and non-infarcted myocardium, promoting MVO. It was recently shown that CRP is independently associated with 4 months infarct size reduction, underscoring a pathophysiological interplay between inflammation and adverse infarct healing in survivors of acute STEMI [33]. Myocardial cell necrosis per se is recognized as a powerful proinflammatory stimulus [34]. This implicates that a larger infarct size may induce an increased inflammatory response and higher levels of CRP. CRPv, a time-dependent inflammatory marker, might help to better characterize inflammatory process dynamics during myocardial infarction [10]. In a retrospective analysis, CRPv was suggested to be related to short-term mortality after STEMI [10]. CRPv might not only play a role in the occurrence of adverse events, but it might also be associated with an increased risk for new onset atrial fibrillation after revascularized STEMI [35]. However, more research in this field is warranted.

We measured CRP and cTnT from admission to day 4 and could confirm and expand previous findings by showing that CRP and cTnT peaked in median at 47 h and 11 h, respectively, after admission for

STEMI in the overall cohort [36]. CRPv, as determined from admission and 24 h CRP values, emerged as strong and independent predictor of MVO. This allows MVO to be predicted earlier and eliminates the need to wait for peak CRP, which is available at a later time point (~day 2 to 3). Furthermore, the predictive value of peak cTnT in addition to peak CRP was not higher compared to peak cTnT in combination with CRPv. This supports the use of CRPv very early after primary PCI (1 day) as early and sensitive predictor of more severe microvascular tissue injury.

Experimental studies have suggested that inhibiting CRP in acute myocardial infarction might minimize myocardial damage [27]. In a rat model of coronary occlusion, a small molecule, 1,6-bis (phosphocholine)-hexane, a specific inhibitor of human CRP, restricted the extent of infarct size following human CRP injection [28]. According to Sheriff et al. [37] selective CRP-apheresis led to reduction of CRP plasma levels by 50–60% resulting in an impressive decrease of myocardial infarct volume as visualized by CMR. Our findings further underscore this hypothesis and suggest that treatment strategies to lower CRP values could be of clinical interest to potentially reduce overall IS and minimize the risk for MVO [27,28,37,38]. Dedicated research around CRPv as a very early and robust marker for an excessive inflammatory response seems warranted. In particular, the question arises whether these high-risk patients could benefit from early and targeted intervention aimed at lowering CRP after PCI.

4.1. Limitations

Only stable STEMI patients with Killip class <3 and a delay <12 h were included in this analysis. Notably, the vast majority of STEMI patients present with Killip class <3 [39]. The predictive value of CRPv on MVO might thus not be applicable to unstable patients or NSTEMI. Our findings are not applicable to patients with an increased admission CRP value (above 15 mg/l), which are, however, a very small minority of patients (<4%). Intramyocardial hemorrhage as determined by T2* mapping is increasingly recognized as important marker for severe microvascular infarct pathology with strong prognostic implications [40]. In this study, T2* mapping was not available for all patients and we can therefore not assess the potential association between CRPv and intramyocardial hemorrhage. Further studies with a larger number of patients are necessary to investigate the prognostic value of CRPv for hard clinical endpoints and to define its best cut-off value.

5. Conclusions

In patients treated with PCI for acute STEMI, CRPv emerged as strong, independent and incremental predictor of MVO. These data indicate that CRPv, in addition to cTnT, may improve early risk assessment in this population.

Abbreviations

| | |
|------|------------------------------------|
| AUC | Area under the curve |
| CI | Confidence interval |
| CMR | Cardiac magnetic resonance |
| CRP | C-reactive protein |
| CRPv | C-reactive protein velocity |
| cTnT | Cardiac troponin T |
| ECG | Electrocardiogram |
| H | Hours |
| Hs | High-sensitivity |
| IQR | Interquartile range |
| IS | Infarct size |
| LGE | Late gadolinium enhancement |
| LV | Left ventricular |
| LVEF | Left ventricular ejection fraction |
| LVMM | Left ventricular myocardial mass |
| MACE | Major adverse cardiac events |
| Min | Minutes |

| | |
|-------|---------------------------------------|
| MVO | Microvascular obstruction |
| PCI | Percutaneous coronary intervention |
| ROC | Receiver operating characteristic |
| STEMI | ST-elevation myocardial infarction |
| TIMI | Thrombolysis in myocardial infarction |

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Author statement/Contribution of authors

MH: study conception and design; analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript.

CT: analysis and interpretation of data; revising critically for important intellectual content; final approval of the manuscript.

MR: analysis and interpretation of data; revising critically for important intellectual content; final approval of the manuscript.

IL: analysis and interpretation of data; revising critically for important intellectual content; final approval of the manuscript.

FT: analysis and interpretation of data; revising critically for important intellectual content; final approval of the manuscript.

MH: analysis and interpretation of data; revising critically for important intellectual content; final approval of the manuscript.

AM: analysis and interpretation of data; revising critically for important intellectual content; final approval of the manuscript.

CB: analysis and interpretation of data; revising critically for important intellectual content; final approval of the manuscript.

GK: analysis and interpretation of data; revising critically for important intellectual content; final approval of the manuscript.

AB: analysis and interpretation of data; revising critically for important intellectual content; final approval of the manuscript.

BM: study conception and design; analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript.

SJR (Corresponding author): study conception and design; analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Declaration of Competing Interest

All authors have declared no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2021.06.023>.

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