High-sensitivity C-reactive protein and long term reperfusion success of primary percutaneous intervention in ST-elevation myocardial infarction

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A B S T R A C T

Aims: In STEMI patients, success of reperfusion of primary PCI predicts cardiac remodeling and clinical outcome. This success may depend on inflammation. We aimed to investigate the association between inflammation and reperfusion success, left ventricular function and long-term mortality in STEMI patients.

Methods: In 376 consecutive STEMI patients of the GIPS-III trial hs-CRP levels were measured at baseline, 2 weeks, 7 weeks and 4 months post-PCI. Myocardial blush grade was used to determine success of myocardial reperfusion. In multivariate models sex, age, hs-CRP levels at baseline, NT-proBNP levels at baseline, ischemia time, heart rate, TIMI flow, and CK, CKMB and troponin AUC were included. Follow-up was complete until 4 months.

Results: Baseline hs-CRP levels were 2.1 mg/l (IQR 0.5–4.2 mg/l). hs-CRP levels were associated with impaired reperfusion (OR 1.239, 95% CI 1.006–1.527) and remained higher compared to patients with normal reperfusion up to 2 months after PCI (hs-CRP 1.9 mg/l (IQR 0.9–3.7 mg/l) versus 1.5 mg/l (IQR 0.7–2.7 mg/l), p = 0.041). In multivariate analysis baseline hs-CRP levels remained independently associated with impaired reperfusion. In patients with impaired reperfusion, hs-CRP and NT-proBNP levels remained higher during 4 months of follow-up. No correlation was observed between hs-CRP at baseline and left ventricular function at 4 months. The number of events was small and we observed no differences in mortality.

Conclusion: Increased hs-CRP levels at presentation are associated with impaired microvascular reperfusion after PCI in STEMI patients and remain higher until 2 months follow-up.

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1. Introduction

In patients with acute myocardial infarction (AMI) morbidity and mortality remains high despite advances in treatment like timely reperfusion of coronary stenosis by primary percutaneous coronary intervention (PCI). After AMI left ventricular function is often impaired due to impaired left ventricular remodeling and results in heart failure (HF) [1–3]. Inflammation is considered to play a substantial role in the pathophysiological process of cardiac remodeling [4,5]. AMI triggers a systemic acute-phase response, in which neutrophils and monocytes/macrophages track to the infarcted region of the heart [2]. Epidemiological studies suggest that circulating concentrations of inflammatory markers, such as C-reactive protein (CRP) are associated with subsequent risk of atherosclerosis formation, coronary heart disease (CHD) and cardiac remodeling. In the setting of an AMI elevated CRP levels on admission are associated with impaired myocardial reperfusion as depicted by lower Thrombolysis in Myocardial Infarction (TIMI) flow grades [6–9]. A clear difference in CRP patterns between different forms of acute coronary syndrome (ACS) was previously described in the early days after admission [10]. Currently, sparse data is available about time course of CRP levels and its association with reperfusion success after AMI. The aim of this study was to investigate the association between inflammation, as determined by high sensitivity C-reactive protein (hs-CRP), and reperfusion success, left ventricular function and long-term mortality in patients with ST elevation myocardial infarction (STEMI).

2. Methods

2.1. Study population and design

We included all patients participating in the GIPS-III trial. This trial was designed to evaluate the effect of metformin treatment on preservation of left ventricular function in STEMI patients without diabetes. Details on the design of the GIPS-III trial have been reported previously [11]. In brief, all patients admitted to the University Medical Center Groningen between January 1st, 2011, and May 26th 2013, via the STEMI protocol were considered eligible for the trial. Inclusion criteria were age older than 18 years, the presence of STEMI, and primary PCI with implantation of at least 1 stent with a diameter of at least 3 mm resulting in TIMI flow grade 2 or 3 post PCI. Major exclusion criteria were previous
myocardial infarction, known diabetes, the need for coronary artery bypass graft surgery, severe renal dysfunction, and standard contraindications for magnetic resonance imaging (MRI) [12]. The study protocol of the GIPS-III trial was in accordance with the Declaration of Helsinki and was approved by the local ethics committee ( Groningen, the Netherlands) and national regulatory authorities. Informed consent was obtained for inclusion of the patients.

2.2. Data collection

On admission, standard laboratory assessment was performed and standard physical examination parameters were measured according protocol. Patients were seen in the outpatient clinic 2 weeks, 7 weeks, 4 months, and one year after discharge.

During hospitalization, blood was sampled at baseline (initial admission) and at 3, 6, 9, 12, and 24 h after PCI to monitor values of cardiac enzymes and high sensitive troponin. Less frequently during hospitalization and at every visit to the outpatient clinic heamoglobin, leucocytes (including neutrophils, lymphocytes), platelets, glucose, hs-CRP and N-terminal pro B-type natriuretic peptide (NT-proBNP) were determined. Furthermore, during PCI 24 h after PCI, and at every visit to the outpatient clinic, blood samples for additional analyses were collected [11]. The incidence of major adverse cardiac events (MACE; the combined end point of death, reinfaction, or target-lesion revascularization) was recorded until 4 months.

hs-CRP was assayed by nephelometry with a lower limit of 0.175 mg/l (BNII N; Dade Behring, Marburg Germany). A hs-CRP level below 1 mg/l was considered as normal [13]. Leucocytes were determined on the XE2100 – system (Sysmex, Japan). As the neutrophil/lymphocyte ratio is associated with cardiovascular outcomes, we calculated this ratio as well [14]. NT-proBNP levels were examined (Roche (Modular, Germany)), as NT-proBNP is known as a biomarker for the development of HF and inflammation is thought to play a role in the development of HF [15]. Furthermore, we calculated the ratio between hs-CRP and NT-proBNP levels evaluating whether these ratios would be different between reperfusion groups.

2.3. Myocardial blush grade

Myocardial blush grade (MBG) represents an angiographic measurement of myocardial perfusion [16]. It reflects myocardial response to ischemic injury and reperfusion. MBG was categorized as follows: 0 = no myocardial blush, or contrast density; 1 = minimal myocardial blush; 2 = moderate myocardial blush but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery; 3 = normal myocardial blush comparable to that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery [17]. The patients were categorized as having normal (MBG 3) versus impaired (MBG 0–2) reperfusion. Coronary angiograms were analysed by two physicians blinded to clinical data.

2.4. Statistical analysis

Continuous variables were summarized as mean ± standard deviation if normally distributed or median and interquartile range if skewed. Discrete variables were presented as frequencies and percentages. To compare groups, we used Student’s t-test for normally distributed continuous variables, Mann–Whitney U test for skewed continuous variables, Chi-square and Fisher’s exact test for categorical variables. In order to be able to compare hs-CRP levels within reperfusion groups (between consecutive time points) and between reperfusion groups on the same time points, we used mixed model analysis. We modeled hs-CRP using a random intercepts regression model in terms of MBG and time points. Area under the curve (AUC) and peak values were calculated over the first 72 h post-PCI using the trapezoid method as previously described. No curve was calculated for patients having <2 measurements or only measurements with a timespan of <10 h. In multivariate models (logistic regression) for impaired reperfusion (impaired vs. normal), sex, age, hs-CRP levels at baseline, NT-proBNP levels at baseline, ischemia time, heart rate, TIMI flow (pre- and postintervention), and CK, CKMB and troponin AUC were included. Statistical significance was considered at a 2-tailed p-value of <0.05. Statistical analyses were performed with Stata version 13.0 (StataCorp).

3. Results

3.1. Study population

From 1 January 2011 – 26 May 2013, 376 out of 1473 patients admitted to the hospital via the STEMI protocol were included in the analysis [12]. Baseline characteristics are presented in Table 1.

Clinical characteristics did not significantly differ between patients with impaired and normal reperfusion. The average age was 59 ± 12 years and 25% were female. Time between first complaints and catheterization, i.e. ischemia time, was longer in patients with impaired reperfusion than in patients with normal reperfusion. Levels of CK, CK-MB, and NT-pro BNP at admission were higher in patients with impaired reperfusion than in patients with normal reperfusion. Furthermore, levels of leucocytes and neutrophils, and the neutrophil/lymphocyte ratio were higher in patients with impaired reperfusion (Table 1).

3.2. Temporal course of hs-CRP

hs-CRP levels are presented in Fig. 1A and B. Levels of hs-CRP decreased over time in both groups. Patients with normal reperfusion had lower hs-CRP levels at baseline, 2 weeks, and 7 weeks compared...
to patients with impaired reperfusion. At 4 months, hs-CRP levels were not significantly different.

### 3.3. hs-CRP and associations

hs-CRP levels at baseline were positively correlated with leucocyte levels at baseline, NT-proBNP levels at baseline, and ischemia time ($r = 0.19, p = 0.001; r = 0.21, p < 0.001; r = 0.22, p < 0.001$, respectively) and negatively correlated with myocardial reperfusion ($r = -0.12, p = 0.035$) (Table 2). After multivariate adjustment, higher hs-CRP levels at baseline remained positively associated with impaired reperfusion. Higher infarct-related artery TIMI flow (postintervention) had a negative association with impaired reperfusion (Table 3).

### 3.4. Temporal course of hs-CRP, NT-proBNP, and CRP/NT-proBNP ratio

Levels of NT-proBNP were higher in patients with impaired reperfusion in time (Fig. 1C). NT-proBNP increased in both groups between baseline and two weeks, these levels decreased thereafter. At 4 months NT-proBNP levels remained higher in patients with impaired reperfusion. Furthermore, ratio between hs-CRP and NT-proBNP levels over time did not significantly differ between groups (Supplemental Fig. 1).

### 3.5. Outcomes

Clinical outcomes at 4 months did not significantly differ between patients with impaired and normal reperfusion (data not provided).

![Fig. 1](https://example.com/fig1.png)

**Fig. 1.** hs-CRP levels and NT-proBNP levels over time in 376 patients with impaired reperfusion and normal reperfusion. Mixed model analysis was used to compare hs-CRP and NT-proBNP levels within and between reperfusion groups. Data are presented as mean and standard error of the mean (SEM). NS = not significant. Fig. 1A depicts the proportion of patients with impaired reperfusion between the lowest (baseline 0–1 mg/l, 2 w 0–0.9 mg/l, 7 w 0–0.8 mg/l, 4 m 0–0.7 mg/l) and highest quartile (baseline > 4.3 mg/l, 2 w >5.0 mg/l, 7 w >3.3 mg/l, 4 m > 2.5 mg/l) of hs-CRP levels. Fig. 1B and C depict hs-CRP and NT-proBNP levels between the reperfusion groups on the same time points. Fig. 1D shows the decrease within reperfusion groups between consecutive time points. hs-CRP remained significantly higher in patients with impaired reperfusion for 7 weeks (Fig. A). NT-proBNP levels were also higher in these patients (Fig. B). Fig. C depicts a combination of Figs. A and B in order to show the parallelism of the biomarkers in both reperfusion groups. Furthermore, hs-CRP levels decreased significantly in both reperfusion groups between 2 and 7 weeks, whereas NT-proBNP levels differed between all consecutive time points (Fig. C).
Table 3
Correlation between hs-CRP at baseline and other variables.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>hs-CRP at baseline</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocytes at baseline</td>
<td>0.19</td>
<td>0.001</td>
</tr>
<tr>
<td>NT-proBNP at baseline</td>
<td>0.21</td>
<td>0.000</td>
</tr>
<tr>
<td>Ischemic time</td>
<td>0.22</td>
<td>0.000</td>
</tr>
<tr>
<td>MBG (0,1,2,3) at baseline</td>
<td>-0.12</td>
<td>0.035</td>
</tr>
<tr>
<td>MBG (reduced vs. normal) at baseline</td>
<td>-0.13</td>
<td>0.029</td>
</tr>
<tr>
<td>Infarct size (%) at 4 months</td>
<td>-0.04</td>
<td>0.533</td>
</tr>
<tr>
<td>LVEF (%) at 4 months</td>
<td>-0.06</td>
<td>0.353</td>
</tr>
</tbody>
</table>

hs-CRP = high sensitivity C-reactive protein; NT-proBNP = N-terminal probrain natriuretic peptide; MBG = Myocardial blush grade; LVEF = Left ventricular ejection fraction.

However, the number of clinical events in overall population was low, mortality rate at 1 year was 0%, reinfarction rate at 1 year was 1.8%.

4. Discussion

This study investigated the temporal course of hs-CRP levels in patients who presented with a first STEMI and treated with primary PCI. The principle findings were as follows. First, higher hs-CRP levels at presentation are associated with decreased reperfusion success and these levels remained higher in patients with impaired reperfusion for up to two months after PCI. Second, hs-CRP at baseline is positively correlated with ischemia time, although the correlation is not strong, and together with TIMI flow an independent predictor for myocardial reperfusion. Third, NT-proBNP levels follow the same trend as hs-CRP in time with slightly higher levels in patients with impaired reperfusion. Last, LV systolic function was preserved in these STEMI patients and we did not observe an association between hs-CRP levels and impaired LV function and/or long term outcomes.

4.1. Temporal course of hs-CRP

Earlier studies suggested that CRP levels in STEMI patients reached their peak values between 36 and 42 h after admission [10]. The degree of inflammation marked by CRP was associated with the degree of myocardial necrosis. We indeed observed an association with ischemia time and impaired reperfusion resulting in increased myocardial necrosis. The ischemic time might, in part, also explain the higher hs-CRP levels in these patients at baseline. We also measured hs-CRP at 2 weeks, 7 weeks and 4 months after admission, and in addition to Patti et al. we report on the temporal course of hs-CRP in STEMI patients [8,9,18,19]. In addition, we used more sensitive assay to determine the hs-CRP levels, allowing detection of CRP below 5 mg/l and facilitating the detection of subtle differences between patients with normal and impaired reperfusion. Currently, it remains to be elucidated why hs-CRP levels continue to remain increased for a substantial long period in patients with impaired reperfusion. It may be a consequence of chronic damage of the microvasculature of the heart and the inability to recover quickly due to impaired reperfusion, which causes the liver to continue producing hs-CRP. Furthermore, inflammation plays a key role in wound healing and scar formation after myocardial infarction [20]. Perhaps this reparative mechanism and the remodeling of the heart takes longer in patients with impaired reperfusion, which causes the liver to produce hs-CRP for a longer period. In addition to increased hs-CRP levels in patients with impaired reperfusion, the increased levels of leucocytes, neutrophils, and their ratio in these patients suggest that these patients have a higher inflammatory state. As the significant difference in hs-CRP levels between the impaired and normal reperfusion persists until 7 weeks after admission, and reperfusion success is negatively correlated with infarct size and positively correlated with left ventricular ejection fraction, it could be important to continue monitoring hs-CRP levels until at least 7 weeks [21]. Although this study does not show a direct association between hs-CRP levels and left ventricular function, monitoring these levels could still be of importance, since increased hs-CRP levels in STEMI patients with mildly impaired left ventricular function are associated with adverse cardiovascular events [22]. However, it remains important to critically consider the possible function of hs-CRP [23]. Furthermore, in this study they seem to correspond with the kinetics of NT-proBNP, which might still implications a potential association between inflammation and HF. The ability to evaluate hs-CRP levels and to detect subtle differences over time in such a number of patients is of additional value to previous studies [10].

4.2. hs-CRP and ischemia time as predictors for reperfusion

hs-CRP at baseline is an independent predictor for reperfusion success. This result is consistent with recent studies showing the association of elevated CRP levels at baseline and impaired reperfusion in STEMI patients [8,9]. However, we studied whether subtle differences in hs-CRP, measured with a high-sensitive array allow differentiating between patients with normal and impaired reperfusion. A doubling in hs-CRP level remains an independent predictor for impaired reperfusion after multivariate adjustment, together with impaired TIMI flow (postintervention). It might be plausible that these findings (hs-CRP and impaired TIMI flow) are linked because of a higher risk of peri-procedural myocardial infarction in patients with higher CRP levels at baseline [24].

Previous data suggested that a higher level of hs-CRP (≥23 mg/l) is an independent predictor of long-term clinical outcomes in late-presenting STEMI patients (i.e. ischemia time ≥6 h) [18]. We investigated whether ischemia time, hsCRP and reperfusion were associated. Ischemia time was positively correlated with hs-CRP levels, hs-CRP was negatively correlated with reperfusion, and ischemia time was negatively correlated with reperfusion. Although most of our patients reported a shorter
ischemia time than 6 h, patients with impaired reperfusion reported longer ischemia time than patients with normal reperfusion. However, ischemia time did not remain an independent predictor for poor reperfusion after multivariate adjustment. It is reasonable to assume that ischemia time influences hs-CRP levels and thereby indirectly influences the extent of reperfusion after PCI, and that hs-CRP and TIMI flow are stronger predictors for reperfusion than ischemia time.

4.3. hs-CRP as surrogate biomarker for the development of HF?

In addition to the measurements of hs-CRP levels at different time points, we evaluated NT-proBNP levels measured at same time points. Interestingly, similar to the differences in hs-CRP levels between the reperfusion groups, NT-proBNP levels were also higher over time in patients with impaired reperfusion. Currently, many studies report on the role of inflammation in the development of HF [15,25,26]. Because of the potential association between inflammation and HF, we considered the similarity of the patterns of hs-CRP and NT-proBNP in both reperfusion groups as an interesting phenomenon. It seemed interesting to investigate in which way the hs-CRP levels and NT-proBNP levels correspond to each other, not only at one moment, but also for a longer time period, and whether the association between these levels would differ between reperfusion groups. One way to do this is to calculate the ratio between these levels. The hs-CRP/NT-proBNP ratio at baseline in the normal reperfusion group does not differ from the ratio in the impaired reperfusion group. This is in accordance with the separate hs-CRP and NT-proBNP levels, because levels of both biomarkers are higher in the impaired reperfusion group, and implies that a similar process is going on in these patient groups. As it seems that the kinetics of hs-CRP corresponds with the kinetics of NT-proBNP, hs-CRP could be used as an appropriate biomarker to monitor STEMI patients for the development of HF since it is likely to represent the same pathophysiological process as NT-proBNP. This finding, in addition to the increased leucocyte levels and neutrophil levels, provides a little more insight in the possible link between inflammation and HF development.

4.4. Limitations

Some limitations should be taken into consideration. The GIPS III study consisted of non-diabetic patients presenting with a first STEMI and as a consequence of rapid primary PCI the myocardial infarct size was limited and their systolic LV function well preserved. Possibly, small infarct size and preserved LV-function resulting in limited variation might explain why we did not observe an association between hs-CRP and systolic LV-function. Besides, this was a single-center study in a specific STEMI population with a high proportion of TIMI-3 flow before intervention and our observations should be carefully extrapolated to other populations. Furthermore, our study was not designed to translate hs-CRP levels to clinical decision making and therefore, our results are not readily applicable to the clinical arena in terms of relevance for patient management. However, the observed subtle differences in hs-CRP between reperfusion groups and the phenomenon of resembling the kinetics of NT-proBNP does provide data that might be of mechanistic insight. Although the mechanism between inflammation and reperfusion is not fully elucidated yet, we hope that we gained a little more insight in this mechanism with our findings and that further research could continue with revealing this mechanism. In addition, due to the nature of the condition studied, hs-CRP was not measured before presentation. These data could have added more information about the involvement of inflammation in plaque rupture and the time course of hs-CRP.

4.5. Future perspectives

As hs-CRP is just one marker in the inflammation network, it is necessary to investigate more participants in the inflammatory cascade. It is interesting to dig further into the mechanisms of other inflammatory markers and to evaluate their course after intervention for STEMI. Currently, we see a difference in biomarker levels between patients with impaired and normal reperfusion for a longer time period. As the current follow-up is not very long, we could just speculate on longer term outcomes. In a few years, we have more information about these patients and are hopefully able to state whether differences in biomarker level influences long term outcomes in patients with impaired and normal reperfusion.

5. Conclusion

Higher hs-CRP levels at presentation are associated with lower reperfusion success and higher NT-proBNP levels. Impaired reperfusion is also associated with long-term higher hs-CRP levels compared to optimal reperfusion. Advancing our understanding of the temporal course of inflammatory markers in STEMI provide new insights required to further develop novel strategies of treatment. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.08.027.

Conflict of interest

None declared.

References


