The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/199050

Please be advised that this information was generated on 2020-03-28 and may be subject to change.
A multi-site coronary sampling study on CRP in non-STEMI: Novel insights into the inflammatory process in acute coronary syndromes

Sander A.J. Damen a,*, Gilbert E. Cramer a, Hendrik-Jan Dieker a, Helmut Gehlmann a, Wim R.M. Aengevaeren b, Ton J.M. Oude Ophuis c, Marion J. Fokkert d, Lambert D. Dikkeschei d, Wim H.M. Vroemen e, Freek W.A. Verheugt a, Marc A. Brouwer a, Harry Suryapranata a

a Department of Cardiology, Radboud University Medical Center, Geert Grooteplein Zuid 10, 6525 GA, Nijmegen, the Netherlands
b Department of Cardiology, Rijnstate Hospital, Wagnerlaan 55, 6815 AD, Arnhem, the Netherlands
c Department of Cardiology, Canisius Wilhelmina Hospital, Weg Door Jonkerbos 100, 6532 EZ, Nijmegen, the Netherlands
d Department of Clinical Chemistry, Isala Clinics, Dr. van Heesweg 2, 8025 AB, Zwolle, the Netherlands
e Central Diagnostic Laboratory, Maastricht University Medical Center, P. Debyelaan 25, 6202 AZ, Maastricht, the Netherlands

HIGHLIGHTS
● In NSTEMI patients, there was a trans-cardiac decrease in CRP across the myocardium.
● This decrease was irrespective of time of presentation, infarct size and culprit lesion location.
● There was no trans-lesional gradient across the culprit coronary artery lesion.
● Both injured and non-injured myocardium contributes to the decrease in CRP.

ARTICLE INFO
Keywords:
NSTEMI
C-reactive protein
Inflammation
Coronary sinus

ABSTRACT
Background and aims: Inflammation has become a key element in cardiovascular disease, and recently, new anti-inflammatory interventions have shown promising results. In this context, CRP levels have been thoroughly studied in vitro and in animals, but studies in humans are scarce and insights into its release, site(s) of production and uptake are not uniform.

Methods: We performed a biomarker study with multi-site sampling in the coronary circulation, in non-ST elevation MI (NSTEMI) patients with coronary angiography and right-sided catheterisation. Trans-lesional gradients were obtained by sampling distal to the culprit lesion, in patients with a suitable anatomy. To assess trans-cardiac gradients, blood was sampled from the systemic circulation, coronary sinus (CS) and great cardiac vein. Concentrations of CRP were measured with a high-sensitivity assay.

Results: In 42 patients, a median systemic venous CRP concentration of 4.97 mg/L was observed. There was no evidence of a trans-lesional gradient (4.59 mg/L versus 4.56 mg/L, p = 0.278; n = 14). A significant decrease in CRP concentration was observed between systemic arterial and CS samples (4.88 mg/L versus 4.44 mg/L, p < 0.001; n = 42). This trans-cardiac gradient was irrespective of time of presentation, infarct size and culprit lesion location. The gradient was not only driven by blood that ran through the injured myocardium, but also by lower CRP concentrations in the coronary veins that drain non-infarcted myocardium.

Conclusions: In the context of NSTEMI, we observed a trans-cardiac decrease in CRP, which may indicate the first human in vivo proof of a net CRP uptake by the myocardium, with a role for CRP both in the injured and adjacent myocardium.

1. Introduction
The inflammatory process has become a key issue of interest in the development of atherosclerosis and the progression to atherothrombosis [1–3]. Despite clear associations between C-reactive protein (CRP) and the risk of future events in coronary artery disease [4,5], the

https://doi.org/10.1016/j.atherosclerosis.2018.09.024
Received 1 June 2018; Received in revised form 14 September 2018; Accepted 18 September 2018
Available online 19 September 2018
0021-9150/ © 2018 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).
role of CRP in the acute phase of myocardial infarction still requires further investigation.

In general, there is consensus that CRP production mainly occurs in the hepatocytes in response to an extra-hepatic stimulus [6]. Moreover, systemic CRP levels are generally higher in myocardial infarction (MI) patients than in stable coronary artery disease [7]. Appreciating that CRP binds to injured cells and activates inflammation, an evident role for CRP was suggested in the aftermath of MI [7]. Several studies focused on coronary CRP levels, varying from trans-lesional assessments (proximal and distal to the culprit lesion) [8–12] to studies on trans-cardiac gradients, i.e. from the aorta to the coronary sinus (CS) [12–17].

Despite evidence of high CRP mRNA content in unstable plaques [13] and a trans-lesional increase of CRP in patients with unstable angina [12], other studies on trans-lesional concentrations generally reported no evidence of a gradient in acute coronary syndrome (ACS) [9–11]. The few studies on trans-cardiac gradients showed conflicting results and varied in study design and population [12–17]. Although several histopathological studies have shown that CRP is deposited in infarcted regions of the myocardium [18,19], most studies on trans-cardiac gradients did not report on the association between the extent of myocardial damage and CRP changes. This may be of particular importance, as previous studies have suggested that the trans-cardiac gradient of inflammatory markers depends on the presence or absence of injured myocardium [20,21]. In this context, a more detailed study could improve insight into the role of CRP in MI patients.

We therefore conducted a multi-site coronary sampling study in non-ST elevation MI (NSTEMI) patients to assess both trans-lesional and trans-cardiac CRP gradients. In the abovementioned context, we focussed on the impact of single versus multivessel disease, infarct size and had specific interest for injured versus non-injured myocardium on changes in CRP levels across the heart.

2. Patients and methods

2.1. Patient population

The Trans-cardiac Assessment of Myocardial Injury and Coronary Inflammation (TRAMICI) study is a prospective mechanistic study performed in the catheterisation laboratory of the Radboud University Medical Center (Radboudumc, Nijmegen, The Netherlands) in patients presenting with a NSTEMI. Patients from the Radboudumc and three referring centers were eligible if they presented early after symptom onset, were diagnosed with a NSTEMI and had evidence of elevated (i.e. above the 99th percentile reference limit of normal) and rising cardiac troponin levels based on conventional troponin assays used in the respective hospitals. Subsequently, patients were referred for a clinically indicated coronary angiography (CAG) in the Radboudumc. Upon identification of the culprit coronary artery by the interventional cardiologist, patients were included and study procedures were started. Exclusion criteria were: an indication for emergency percutaneous coronary intervention (PCI) at presentation, prior PCI or CABG (<3 months), prior anginal complaints (<3 weeks), killip class III and IV, other suspected life-threatening disease at presentation, peripheral arterial disease (Fontaine III and IV), presence of a pacemaker, main stem stenosis (>50%), anomalous coronary anatomy, serum creatinine >150 μmol/L, systemic infection, hematologic disorder or treatment with an immunosuppressive agent, treatment with NSAID or antibiotics. The presence of collateral coronary artery filling was considered a relative exclusion criterion. After obtaining oral informed consent prior to the procedure, participants provided written informed consent. The protocol was approved by the local ethical committee and study procedures were in accordance with the Declaration of Helsinki.

2.2. Study procedures

The coronary venous anatomy was recorded during CAG by filming the complete washout of contrast dye. Access to the CS was gained by means of a right-sided catheterisation procedure. For cannulation and blood sampling of the coronary venous system, a Terumo wire (Terumo Europe NV, Leuven, Belgium) and CHAMP multipurpose catheter (Medtronic, Santa Rosa, CA, USA) were used, respectively.

Coronary venous system samples: After cannulation of the CS, the CHAMP catheter was advanced into the great cardiac vein (GCV). This vein primarily drains blood from the anteroseptal walls [22]. Consequently, in patients with a culprit lesion in the left anterior descending artery (LAD), a selective blood sample from this site represents biomarker concentrations in blood that just ran through injured myocardium. Alternatively, in patients with a non-LAD culprit lesion, a selective blood sample from this site represents biomarker concentrations in a vein that drains blood from myocardium not supplied by the infarct related artery. After sampling in the GCV, the catheter was pulled back towards the CS at the point where the middle cardiac vein merges with the CS. Being the rendezvous point of all blood that passed the myocardium, the CS sample represents the trans-cardiac gradient.

Blood sampling was performed according to the following protocol driven procedures. First, the position of the catheter was confirmed using contrast dye, after which the catheter was flushed. Second, there was a waiting period to allow for sufficient blood reflux. Then, a first blood sample of 3–4 mL was drawn to perform blood gas analysis, as a double check of the catheter position. Subsequently, the blood sample of interest was obtained. Fig. 1 illustrates the different sampling sites within the coronary venous system.

Systemic blood samples: After removal of the CHAMP catheter from the coronary venous system, systemic blood samples were obtained from the femoral venous and arterial sheaths.

Culprit artery samples: Patients with a suitable anatomy, and in whom the preferred revascularisation strategy was PCI, were eligible for an additional sample from the culprit coronary artery distal to the culprit lesion. Prior to the PCI, a guiding catheter was inserted in the ostium of the culprit coronary artery. A wire was then advanced beyond the culprit lesion followed by an over-the-wire balloon (MAVERICK) or microcatheter (Boston Scientific, Marlborough, MA, USA). After removal of the wire while keeping the catheter in place, blood was aspirated distal from the culprit lesion.

Follow-up samples: Finally, at 6 and 12 h post-procedure, additional venous samples were obtained from an antecubital vein.

All collected blood samples were divided over serum and plasma tubes, centrifuged, aliquoted and stored at −80 °C until thawed for further analysis.

2.3. Coronary angiography

All angiograms were reviewed by a second team of doctors (SD, GC and HG), unaware of biomarker analysis. They performed a standardised evaluation of left ventriculography for wall motion abnormalities, lesion characteristics, and coronary flow to identify the culprit lesion. Lesion severity was based on visual estimation. In case of a discrepancy with regard to the decision on the culprit artery between the interventional cardiologist and the second team, data were analysed by a third cardiologist (MB), unaware of any former decision on culprit location. When the third reviewer agreed with either of the two previous teams, the location of the culprit artery was decided on. If not, the patient was excluded from the present analysis.

2.4. Measurement of biomarkers

Biomarker analysis was performed at the clinical chemistry department in the Isala Clinics (Isala Clinics, Zwolle, The Netherlands) and the Maastricht University Medical Center+ (MUMC, Maastricht,
The biomarkers involved in the current analysis are: high-sensitivity CRP, high-sensitivity cardiac troponin T (hs-cTnT), CK-MB and albumin. All assays were provided by Roche Diagnostics, and analyses performed on a Cobas analyser (Roche, Mannheim, Germany). With respect to CRP concentrations the lower limit of detection is 0.15 mg/L, and at 0.3 mg/L the coefficient of variation is < 10%. The hs-cTnT assay has a limit of blank of 3 ng/L and a coefficient of variation of < 10% at 13 ng/L (limit of quantification). With regard to the CK-MB immunoassay a lower limit of detection of 0.1 ng/mL is reported. Given the well-described correlation between infarct size and peak CK-MB, this biomarker was chosen to define infarct size in our population [23].

Patients were divided in small (lower 50th percentile) and large (upper 50th percentile) MI based on the peak CK-MB concentration measured during admission. As for albumin, the measuring range was 2–100 g/L defined by the limit of detection and the maximum of the master curve.

2.5. Statistical analysis

The present analysis on CRP is a prospectively defined secondary objective of the TRAMICI project, and is performed on a subset of the entire study population. The total number of participants in TRAMICI was based on the required number of patients for the primary objective, with troponin measurements as primary outcome. Continuous data were analysed for Gaussian distribution and were expressed as medians with interquartile ranges (IQR). Numerical data were described as a number with a percentage. Paired data were compared using the Wilcoxon signed rank test. The Mann-Whitney U test was performed for comparisons of biomarker concentrations between subgroups of patients. Fisher’s exact test was used for comparison of proportions of patients. To assess the correlation between the per-patient trans-cardiac CRP and albumin gradients we calculated the Pearson correlation coefficient. A p-value less than 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics software (version 22.0, IBM Corp., Armonk, NY, USA).

3. Results

The study population for the current analysis consists of 42 patients (Supplementary Figure 1). Baseline clinical and angiographic characteristics are shown in Table 1. The median duration of symptoms was 236 (interquartile range: 99–485) minutes, with a median duration of symptom onset to the start of CAG of 25 (19–35) hours. The median baseline peripheral venous concentration of hs-cTnT was 175 (91–314) ng/L, which increased to a median peak concentration of 229 (131–398) ng/L.

3.1. Peripheral CRP concentrations

The CRP concentrations at baseline showed no significant difference between the arterial and venous samples (4.88 [2.35–10.42] mg/L vs. 4.97 [2.29–10.16] mg/L; p = 0.164). The median peripheral venous CRP concentration increased to 5.35 [2.62–13.11] mg/L (p < 0.001) at 6 h and to 6.87 [3.32–12.10] mg/L (p < 0.001) at 12 h after the baseline measurements. At baseline, patients with a large MI had non-significantly higher CRP concentrations compared to small MI patients (7.52 [3.44–41.26] mg/L vs. 5.22 [2.06–11.9] mg/L; p = 0.170).

3.2. Trans-cardiac gradients

CRP concentrations in the CS and systemic circulation are depicted in Table 2. A decrease in median CRP concentration was observed
Concentrations of CRP depicted as medians (IQR) in mg/l. a: comparison between peripheral artery and CS. b: comparison between peripheral artery and GCV.

CRP concentrations in systemic artery, coronary sinus and great cardiac vein.

### Table 1
Baseline clinical and angiographic characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All patients n = 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at admission</td>
<td>65 (53–73)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>32 (76%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>22 (52%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (50%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Aspirin therapy</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>13 (31%)</td>
</tr>
<tr>
<td>History of MI</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>History of coronary revascularisation</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>hs-cTnT on admission (ng/L)</td>
<td>175 (91–314)</td>
</tr>
<tr>
<td>CK-MB on admission (ng/mL)</td>
<td>7.13 (3.0–15.9)</td>
</tr>
<tr>
<td>Time between onset complaints and CAG (hours)</td>
<td>25 (19–35)</td>
</tr>
<tr>
<td>Duration of anginal symptoms (min)</td>
<td>236 (99–485)</td>
</tr>
<tr>
<td>Number of diseased vessels</td>
<td>1 (36%)</td>
</tr>
<tr>
<td>2</td>
<td>19 (45%)</td>
</tr>
<tr>
<td>3</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>Culprit artery</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>RCX</td>
<td>16 (38%)</td>
</tr>
<tr>
<td>LAD</td>
<td>16 (38%)</td>
</tr>
<tr>
<td>Severity culprit stenosis</td>
<td></td>
</tr>
<tr>
<td>50–70%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>70–90%</td>
<td>20 (48%)</td>
</tr>
<tr>
<td>&gt; 90%</td>
<td>22 (52%)</td>
</tr>
<tr>
<td>PCI performed</td>
<td>27 (64%)</td>
</tr>
</tbody>
</table>

Values are medians (interquartile range) or numbers (percentage).

### Table 2
CRP concentrations in systemic artery, coronary sinus and great cardiac vein.

<table>
<thead>
<tr>
<th></th>
<th>Systemic artery</th>
<th>CS</th>
<th>p-value</th>
<th>GCV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 42)</td>
<td>4.88 (2.35–10.42)</td>
<td>4.44 (2.14–9.42)</td>
<td>&lt; 0.001</td>
<td>4.43 (2.23–9.50)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LAD (n = 16)</td>
<td>4.87 (1.33–12.25)</td>
<td>4.65 (1.36–10.87)</td>
<td>0.003</td>
<td>4.80 (1.45–9.60)</td>
<td>0.134</td>
</tr>
<tr>
<td>Non-LAD (n = 26)</td>
<td>4.88 (2.53–10.42)</td>
<td>4.44 (2.31–9.30)</td>
<td>0.002</td>
<td>4.28 (2.39–9.65)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Concentrations of CRP depicted as medians (IQR) in mg/l. a: comparison between peripheral artery and CS. b: comparison between peripheral artery and GCV. CS: coronary sinus. GCV: great cardiac vein. LAD: left anterior descending culprit artery. Non-LAD: right coronary artery or ramus circumflex culprit artery.

3.3. Culprit lesion

In a selected group of 14 patients, blood was obtained from the culprit coronary artery distal to the culprit lesion. No significant difference was observed in CRP concentration between the systemic arterial and post-stenotic compartment sample (4.59 mg/L [2.07–7.73] versus 4.56 mg/L [2.07–7.90], p = 0.278).

3.4. Selective sampling of the great cardiac vein

Patients were categorised according to the infarct related artery, LAD (n = 16) versus non-LAD (n = 26; RCA or RCX). As the GCV selectively drains blood from the anteroseptal wall, measurements of CRP derived from the GCV represent a trans-cardiac gradient across ‘injured’ myocardium for patients with a culprit in the LAD. For patients in the non-LAD group, the measurements reflect a gradient across ‘non-injured’ myocardium. Concentrations of CRP in the GCV are depicted in Table 2.

There was a decrease in CRP concentration towards the GCV, which was only significant in patients with a non-LAD culprit lesion. Relative changes in CRP towards the GCV are depicted in Fig. 2D (light grey boxes).

4. Discussion

In this elaborate multi-site coronary sampling study in patients presenting with an NSTEMI, we showed a significant trans-cardiac decrease in CRP from the systemic circulation to the coronary venous system. At the same time, CRP concentrations across the culprit lesion were not different from those measured in the systemic circulation. Our in vivo finding of a trans-cardiac decrease are in line with ex vivo observation of CRP deposition, and suggest a net uptake at the level of the myocardial tissue.

In general, systemic CRP concentrations are known to increase after MI [24]. This corroborates with our CRP concentrations six and 12 h after the CAG. In view of this, the overall response to myocyte injury in the setting of NSTEMI is that of CRP production. Besides hepatic secretion, several studies also suggested a role for the coronary plaque as a production site for CRP. This was based on an in vitro study that demonstrated CRP production by coronary artery smooth muscle cells [25]. Moreover, an ex vivo experiment showed the presence of CRP mRNA in culprit plaques from patients with unstable coronary artery disease [13]. In accordance with this, it has also been shown that CRP concentrations increased across the culprit lesion in a group of patients with unstable angina [12], and across the coronary circulation (aorta to CS) in another group of patients [13,14]. Based on these observations, it has been suggested that there is local vascular production in addition to systemic production. Interestingly, several other studies investigating trans-lesional gradients did not reproduce an increase of CRP across the culprit lesion and disputed the finding of local vascular production [9–11]. Our study, in which a trans-lesional CRP gradient could not be shown, corroborates with these findings. Additionally, our analyses on the burden of atherosclerotic disease - as expressed by single versus multivessel disease - had no influence on the observed trans-cardiac CRP decrease (Fig. 2). This suggests that the trans-cardiac gradient we
observed is mainly driven at the level of the myocardium. Interestingly, and in contrast to the multi-site sampling procedures in our study, the majority of studies on CRP gradients did not simultaneously assess both trans-lesional and trans-cardiac gradients, which complicates the integration of the available study data into a more comprehensive concept. Moreover, it is important to note that, in contrast to cardiac production, there have also been reports on myocardial CRP uptake in the setting of myocardial injury. In histopathological studies on myocardial tissue of patients who suffered from fatal ST-elevation MI, it has consistently been shown that CRP was deposited in the infarcted parts of the myocardium [18,19,26].

Intriguingly, we are the first to have observed a clear trans-cardiac decrease in an in vivo setting of NSTEMI patients, which suggests a net myocardial CRP uptake. From previous reports on the function of CRP, it is well known that CRP a-specifically binds to injured tissue after exposure of phosphocholine groups, which appear on the cell membrane of necrotic cells. After binding, CRP activates the complement system promoting opsonisation [27,28], and therefore acts as an important pro-inflammatory mediator [19]. CRP provides an early defence mechanism through rapid activation of the innate immune system. By attracting other inflammatory cytokines, it ultimately plays a role as an initial step in the healing process of injured tissues [27].

Given the extra-cardiac production in the presence of MI, and appreciating the physiologic function of CRP, binding to damaged myocardial cells is a plausible explanation for the observed trans-cardiac decrease in CRP concentrations across the myocardium in the present study.

In contrast to our findings, the majority of studies on trans-cardiac gradients found no difference, and two reported an increase in CRP across the heart [12–17]. Appreciating that the reported group effect is a composite of observed individual increases and decreases, we hypothesised that differences in infarct size between studies may have contributed to the discrepant findings. Especially, given the previous evidence that the presence or absence of myocardial injury has an effect on trans-cardiac gradients of inflammatory markers [20,21]. With regard to the impact of the extent of myocardial injury on our observed trans-cardiac gradient, we compared patients with a larger-sized MI to those with a smaller-sized MI according to peak CK-MB concentrations. On average, we observed a decrease in CRP concentration from the systemic circulation to the CS for both groups, irrespective of whether infarct size was based on peak CK-MB, baseline or peak troponin levels (latter two not reported). Interestingly, in a few patients we saw a trans-cardiac increase in CRP. Most of these patients were among those with a larger-sized MI. From this we contemplate that in a different population, represented by patients with larger-sized MIs, trans-cardiac gradients might show net increases in CRP concentration more often. Although speculative, this could be one of the explanations for the non-uniformity of available evidence in ACS [13,14]. Unfortunately, the majority of previous studies did not report on infarct size and the impact on the trans-cardiac CRP gradients. The only study in acute ST elevation MI patients, to our knowledge, that performed CRP measurements in CS blood did not observe a trans-cardiac gradient [15]. Notably, the median time-interval between symptom onset and study procedures was only 3.2 ± 0.5 h, whereas in our study it was 25 [19–35] hours. Importantly, ex vivo examinations of STEMI patients have shown that the process of CRP uptake occurs between 12 h and 5 days after symptom onset. This time-interval is considered the phase of polymorphonuclear leukocyte infiltration [18,19]. Probably, and in contrast to our findings, blood sampling was too early to result in a

![Fig. 2. Trans-cardiac gradients of CRP according to subgroups.](image)
measurable amount of CRP uptake in this study of acute MI patients. Given the aforementioned aspects, future research investigating inflammatory gradients in MI patients should adequately address infarct size and timing between symptom onset and blood sampling.

In contrast to previous studies, our sampling protocol allowed for determination of CRP changes across injured and non-injured myocardium, and we found a decrease in CRP in both subgroups. This demonstrates that non infarcted myocardium is involved in the CRP physiology as well. In support of this observation is an imaging study that showed that high increases in CRP concentration after suffering MI resulted in larger adjacent peri-infarct zones [29]. Interestingly, in a murine study of ischemia and reperfusion, the impact of CRP injections was studied in a controlled design. In the group with injections of CRP, higher rates of apoptosis were not confined to the infarcted part of the myocardium but included the entire area at risk [30]. In addition, in a transgenic mouse model of MI, there was increased macrophage infiltration and apoptosis in the border zones of the infarcted myocardium in the mice with CRP expression [31]. Importantly, an adverse effect on left ventricular function recovery was observed in the mice with versus without CRP expression, despite equal infarct sizes [31]. Therefore, our observation of a decrease in CRP over non-injured myocardium, might be the first in vivo proof of a pathobiological role for CRP in non-infarcted myocardium.

4.1. Implications

Our observations support the hypothesis that CRP binds to myocardial cells in the setting of a NSTEMI. This opens new insights in the role of inflammation in the aftermath of MI. New drugs targeting upstream biomarkers, interacting with the interleukin-CRP axis, are investigated in patients with stable cardiovascular disease (CIRT trial and CANTOS trial) [32–34]. Their target is to slow down the progression of coronary artery disease. In view of the potential roles of CRP in LV remodelling after MI, it remains to be answered whether and how these drugs might interfere with infarct healing. Interestingly, it was shown that the IL-6 receptor antagonist tocilizumab reduced the levels of CRP, and cardiac troponin release after NSTEMI [35]. Notably, together with our findings of a trans-cardiac CRP decrease across the myocardium in the acute phase of myocardial infarction, the concept that more insight in the role of inflammatory processes after ACS might provide novel therapeutic targets is strongly supported [36,37].

4.2. Limitations

Appreciating the mechanistic design of the study, our sample size is limited and therefore results on trans-lesional findings, subgroup analyses, and correction for confounders may have been hampered by lack of statistical power. The present study question concerns a prospectively defined secondary analysis of the TRAMICI protocol, and the primary outcome measure was the within patient difference in the trans-cardiac gradient of CRP. In retrospect, incorporation of more upstream inflammatory biomarkers (e.g. IL-1 and IL-6) would have been interesting to gain additional information on the pathobiology of inflammatory processes in acute myocardial infarction. The observed absence of a trans-lesional CRP difference might have been caused by local catabolism or uptake of CRP in the vessel wall [8]. However, the CRP assay used has high-sensitivity characteristics. Thus, small differences were detectable, even in the setting of relatively high systemic production. Despite several protocol driven precautions, it can not be ruled out completely that dilution may have affected the observed trans-cardiac decrease in CRP in some cases, to some extent. However, prior to actual sampling, the protocol not only dictated a temporal halt, to allow for sufficient blood reflux; it also incorporated a first sample of 3–4 mL for blood gas analysis, before the sample of interest was obtained. To further address this issue, we performed analyses on other plasma proteins, i.e. albumin. In the absence of a per-patient correlation between the trans-cardiac gradients of albumin and CRP, it is unlikely that sample dilution markedly affected our findings. With regard to possible confounders, none were identified for the trans-cardiac CRP gradient. In addition, no difference in trans-cardiac gradient was observed for patients on long-term aspirin and statin use. Finally, our study lacks a control group of patients without evidence of MI. Appreciating the different studies reporting no CRP gradient in patients with stable angina [10,13,14,16], and the expected additional clinical/ scientific benefit in this particular group of patients, we decided not to expose these patients to an invasive, rather extended procedure with an elaborate sampling protocol.

4.3. Conclusion

In the present population of patients with ongoing NSTEMI, we observed a net trans-cardiac CRP decrease in conjunction with increases of CRP in the systemic circulation over time, without evidence of local production at the site of the culprit coronary lesion suggesting myocardial uptake of CRP. Due to elaborate blood sampling from both the systemic and cardiac circulation, we were able to observe that CRP uptake was not limited to the infarcted myocardium but was also prominent in regions adjacent to injured myocardium.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

The laboratory assays were kindly provided to use by Roche diagnostics.

Acknowledgements

We would like to thank Rein van der Sluis, lab technician of the Isala Clinics, for the analysis of the blood samples. We would like to thank Joris Nas M.D. for critically revising the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2018.09.024.

References

