

## Systemic Inflammation after Transradial Coronary Angiogram: Statistically (But Not Clinically) Significant?

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### ABSTRACT

**AIMS:** To evaluate if transradial diagnostic coronary angiogram by itself could lead to a systemic inflammation.

**METHODS:** In 96 patients with baseline hs-CRP level <5 mg/L, venous samples were obtained the day before the procedure and the day after. Coronary angiogram was performed with 4, 5 or 6 French radial access catheters.

**RESULTS:** Mean hs-CRP at admission was 2.3 mg/L  $\pm$  1.4. At day 2, the mean CRP level was 2.7 mg/L  $\pm$  1.9, with a 0.4 mg/L (17%) statistically significant elevation,  $p < 0.0001$ . No radial access complication (thrombosis or hematoma) occurred. The variation of hs-CRP was positively correlated with age ( $r = 0.20$ ;  $p = 0.04$ ), elevation of creatin kinase ( $r = 0.20$ ;  $p = 0.03$ ) and negatively with amount of contrast ( $r = 0.20$ ;  $p = 0.03$ ).

**CONCLUSION:** In patients with diagnostic coronary angiogram performed through radial access, there is a statistically significant elevation of the biological inflammatory response, whose clinical significance remains elusive.

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**Key words:** Radial access; Diagnostic coronary angiogram; Inflammation; CRP

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### Abbreviations

CABG: coronary arteries bypass graft;

CRP: C-reactive protein;

eGFR: Estimated glomerular filtration rate;

LVEF: left ventricular ejection fraction;

PCI: percutaneous coronary intervention

STEMI: ST-elevation myocardial infarction.

### INTRODUCTION

Inflammation is involved in cardiovascular pathophysiology including atherosclerosis<sup>[1,2]</sup>. In patients admitted with myocardial infarction, it is well established that systemic inflammation occurs and participates probably to the myocardial lesions by themselves<sup>[3]</sup>. In patients with ST-elevation myocardial infarction (STEMI) and treated by primary percutaneous coronary intervention (PCI), the peak of C-reactive protein (CRP) is described on day 3<sup>[4]</sup>. It remains unclear whether the PCI by itself could participate to this systemic inflammation. On the first hand, both basic and clinical research have shown that PCI could

lead to an accumulation of an inflammatory infiltrate<sup>[5,6]</sup>. On the other hand the access by itself could be of importance and remains unclear particularly in clinical trials targeting inflammation. Indeed, in case of femoral access, non-exceptional local complications mainly hematomas could occur and could be underestimated especially in case of subclinical manifestation. Consistently, in 26 patients with diagnostic coronary angiograms (without angioplasty) performed through femoral access, a systemic biological inflammatory response has been reported<sup>[7]</sup>. Nevertheless, alternative explanations could be evoked, including the endothelial stress, myocardial subclinical injuries and so on. In the hypothesis of endothelial injury due to the interventional procedure by itself independently of the coronary intervention, similar inflammatory response should then be evidenced. The contribution of the catheterization procedure by itself has not been adequately addressed until now.

The aim of the study was to evaluate if the coronary angiogram by itself, performed through radial access, could lead to a systemic inflammation. To address this question, we evaluated the inflammatory status of patients admitted for coronary angiogram (without angioplasty) performed through radial access.

## MATERIAL AND METHODS

To this purpose, 464 patients have been retrospectively admitted for blood analysis. Blood collection was declared in our Institution. Among 464 patients admitted for diagnostic coronary angiogram, the retrospective analysis allowed to identify 251 patients with values of hs-CRP at both baseline (the day before) and Day 2 (the day after), see Figure 1. All the patients were screened until biological results could be analyzed. 147 patients with a baseline hs-CRP level abnormal were discarded. Among 104 patients with normal baseline hs-CRP, 98 coronary angiograms were performed through a radial access as presented in the Figure 1. Finally, 1 patient treated with corticosteroid for inflammatory rheumatism and 1 patient with infectious endocarditis were excluded. Finally 96 patients were analyzed.

Coronary angiogram was performed in a single center by experienced interventional cardiologists with 4, 5 or 6 French radial access catheters depending on clinical settings (Radiofocus Introducer II<sup>®</sup>, Terumo, Belgium). Judkins catheters were employed for the coronary injections. A non-ionic contrast agent (Xenetics<sup>®</sup>, Guerbet, France or Omnipaque<sup>®</sup>, Ge Healthcare, France) was used in all patients.

Venous samples were obtained the day before (D0) the procedure and the day after (D2). Five millimeters of blood were placed into prechilled tubes as routinely performed.

Biochemistry parameters were performed on Cobas8000<sup>®</sup> analyzer using reagents from Roche (Roche Diagnostics, Meylan, France) with c701<sup>®</sup> module as well as with the e602<sup>®</sup> module for immunoassay. Evaluation of highly-sensitive C-reactive protein (CRP) by the immunoturbidimetric method, creatinine by the enzymatic method and creatine kinase according to the International Federation of Clinical Chemistry–approved method by CK–N-acetylcysteine kinetic measurement (37°C), was carried out at the inclusion (D0) and two days after (D2). The high-sensitivity cardiac troponin T assay was performed on the Cobas 8000/e602<sup>®</sup> analyzer. The lowest concentration measurable at the 10% CV level is 13ng/L and the 99<sup>th</sup> percentile among healthy individuals is 14 ng/L (confidence interval [CI], 12.7-24.9), as claimed by the manufacturer. The LoD is 5.0 ng/L<sup>[8]</sup>. Estimated glomerular filtration rate (eGFR) was computed using the CKD-EPI equation<sup>[9]</sup>. Fibrinogen was measured

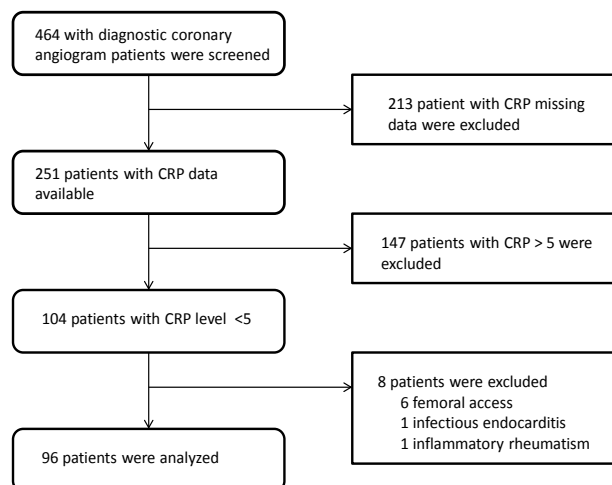


Figure 1 Flow chart.

by immunonephelometry using Von Clauss method (STA Fibrinogen, Diagnostica Stago, Asnières, France).

## Statistical analyses

Data are presented as means  $\pm$  SD when normally distributed and median and interquartile ranges otherwise. The normality of the distribution was estimated by the D'Agostino & Pearson omnibus normality test. For the comparison between hs-CRP at D0 and D2, the Wilcoxon matched-pairs signed rank test was performed. Spearman rank correlation tests were used for the study of potential correlations. Differences were considered statistically significant at the 2-sided  $p < 0.05$  level. All the statistical analyses were performed with the software GraphPad Prism (SAS Institute).

## RESULTS

Among the 96 patients included, 60 (62.5%) were men and the mean age of the population was  $67.5y \pm 12.3$ . Mean hs-CRP at admission was  $2.3 \pm 1.4$  mg/L. Baseline demographic and procedural characteristics of the population are presented in the Table 1 and 2. No radial access complication (thrombosis or hematoma) occurred. At day 2, the mean hs-CRP level was  $2.7 \pm 1.9$  mg/L, with a mean increase of 0.4 mg/L (17%), statistically significant,  $p < 0.0001$  (Figure 2).

Various confounding factors were explored. No correlation was found between hs-CRP variation and individual status of renal function, baseline level of hemoglobin. More importantly, no correlation was evidenced between the variation of hs-CRP and the elevation of hs-troponin when available ( $n=78$ ,  $p=0.98$ ).

The variation of hs-CRP was positively correlated with age ( $r=0.20$ ;  $p=0.04$ ), elevation of creatin kinase ( $r=0.20$ ;  $p=0.03$ ) and negatively correlated with amount of contrast ( $r=0.20$ ;  $p=0.03$ ).

## DISCUSSION

In the present study, we demonstrate for the first time that there is a statistically significant biological inflammatory response in patients admitted for coronary angiogram in spite of the radial access and in spite of the absence of angioplasty.

The systemic biological inflammatory answer is well-established in patients with STEMI, including patients treated successfully

with PCI<sup>[4,10]</sup>. Inflammation could even be involved in the ischemic lesions<sup>[3]</sup>. This is not the case in this population in which there was no myocardial injury detectable with hs-troponin. In various fields of cardiovascular pathophysiology basal level of CRP has been perfectly associated with poor clinical outcomes (references are too numerous to be presented here). In patients with stable coronary artery disease, inflammation has been reported to be correlated with plaque progression<sup>[11]</sup>.

Only rare studies are available on inflammatory answer in patients with coronary angiogram without PCI. In a study on only 13 patients without PCI, CRP was unchanged by contrast with patients with PCI ( $n=23$ ;  $P<0.002$ )<sup>[12]</sup>. In another small study, CRP as well as other inflammatory proteins elevated 24 and 48 hours after PCI in 40 patients with stable angina<sup>[13]</sup>. The elevation was statistically significant from 0.3 until 2.2 mg/L, but the clinical signification of mild elevation of CRP remains probably negligible in routine. Impact of myocardial lesions in case of PCI is not clearly established<sup>[14]</sup>.

There are few data specifically addressing systemic inflammatory answer in patients with coronary angiography though femoral access. In a study on various closure devices, the authors reported in 4 patients an isolated elevation of interleukin 6 but not CRP<sup>[15]</sup> at 6 hours. Studies on the topic include generally only few patients and demonstrate a mild elevation in case of PCI<sup>[16]</sup>.

Importantly, the only one study comparing the biological inflammatory response in patients with or without PCI is a small study on 26 patients with stable angina and admitted for a diagnostic coronary angiogram<sup>[7]</sup> performed through femoral access. The coronary angiogram was shown to trigger a systemic inflammatory response<sup>[7]</sup>. In this study, patients underwent either coronary angiogram ( $n = 13$ ) or coronary angiogram followed by PCI ( $n = 13$ ). There was a significant increase in CRP levels at 24 and 48 hours in both the coronary angiography ( $p < 0.05$ ) and PCI ( $p < 0.01$ ) groups. This result was corroborated by the IL-6 levels (but not the TNF-alpha levels) peaked at 24 hours in both the coronary angiography ( $p = 0.01$ ) and PCI ( $p < 0.005$ ) groups. More importantly, the median elevation of CRP was 2.8 mg/L in the angiogram alone group (baseline 2.8 [1.8-5.5]), hence a low clinical significance. At 4 weeks, both CRP and IL-6 returned to baseline levels. Importantly, the magnitude of the rise of CRP levels was not significantly different between the groups (ie with or without PCI). The authors concluded that an uncomplicated diagnostic coronary angiography triggers a systemic inflammatory response in patients with stable angina. The contribution of coronary angiography should be considered in interpreting the significance of the systemic inflammatory response observed after PCI. In this important article, patients with groin hematoma were discarded from analysis, as well as patients with biological myocardial injury evaluated on troponin release. In our study, hs-troponin has been employed, so that we are probably stricter on this parameter. The baseline CRP was 2.8 mg/L (IQR: 1.8-5.5) suggesting that patients with mild biological inflammation at baseline (CRP>5mg/L) have been also included. Our study differs since patients with a baseline CRP level>5 mg/L were excluded. Median elevation of CRP in the coronary angiogram group was 1.6 mg/L, at day 1 that is 43%, statistically significant. Nevertheless, statistical significance does not mean clinical significance. The elevation is mild and in routine practice this kind of biological result is not taken into consideration. Importantly in our study the elevation is similar at about 0.4 mg/dL (17%) at day 1.

The CRP level is considered only at D0 and D2 although the elevation is even more important numerically at D3 in the work of Golberg *et al*<sup>[7]</sup>.

**Table 1** Patient characteristics on admission.

Characteristics (n=96)	
Male, n (%)	60 (62.5)
Age (y), mean $\pm$ SD	67.5 $\pm$ 12.3
Hypertension, n (%)	54 (56.3)
Diabetes mellitus, n (%)	24 (25)
Smoker, n (%)	18 (18.8)
Dyslipidemia, n (%)	44 (45.8)
Chronic kidney failure, n(%)	3 (3.1)
Prior PCI, n (%)	22 (22.9)
Prior CABG, n (%)	1 (1)
LVEF	
$\leq$ 30%, n (%)	4 (4.2)
31-45%, n (%)	17 (17.7)
> 45%, n (%)	72 (75)
Creatinine ( $\mu$ mol/L), mean $\pm$ SD	96.7 $\pm$ 44.3
Creatinine clearance (mL/min), mean $\pm$ SD	71 $\pm$ 22.6
Hemoglobin (g/dL), mean $\pm$ SD	13.5 $\pm$ 1.9
Hs-CRP (mg/L), mean $\pm$ SD	2.3 $\pm$ 1.4
Fibrinogen (g/L), mean $\pm$ SD	3.8 $\pm$ 0.8
Troponin (ng/mL), mean $\pm$ SD	39.8 $\pm$ 95.8
Creatine kinase (IU), mean $\pm$ SD	139.9 $\pm$ 111
Antiplatelet therapy (APT)	
Acetylsalicylic acid, n (%)	45 (46.9)
P2Y12 inhibitor, n (%)	24 (25)
Statins, n (%)	48 (50)
ACE inhibitors, n (%)	55 (57.3)
B-blockers, n (%)	47 (49)
Calcium channel blockers, n (%)	12 (12.5)

CABG: coronary arteries bypass graft; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention.

**Table 2** Procedural characteristics.

Radial access, n (%)	
Fluoroscopy time (min), mean $\pm$ SD	4.6 $\pm$ 0.34
X-ray dose (cGy/cm <sup>2</sup> ), mean $\pm$ SD	2761 $\pm$ 2072
Amount of contrast (mL), mean $\pm$ SD	63.1 $\pm$ 18.3
Contrast	
Omnipaque®, n (%)	24 (25)
Xenetix®, n (%)	62 (64.6)
Other	3 (3.1)
Ventriculography, n (%)	40 (41.7)
Sheath size	
4 French, n (%)	40 (41.7)
5 French, n (%)	32 (33.3)
6 French, n (%)	24 (25)
Left coronary catheter	
JL 3.5, n (%)	71 (74)
JL 4, n (%)	18 (18.8)
Other, n (%)	7 (7.3)
Right, n (%)	
JR 4, n (%)	90 (93.8)
JR 5, n (%)	1 (1)
Other, n (%)	5 (5.2)
Calcium channel inhibitor, n (%)	59 (61.5)
Vasodilator, n (%)	56 (58.3)
Heparin, n (%)	60 (62.5)
Access site complications	
Hematoma, n (%)	0 (0)
Thrombosis, n (%)	0 (0)

Several mechanisms could lead to this systemic inflammatory answer. First, local tissue damage is possible although radial access offers a minimally invasive approach. The radial puncture and the introducer insertion could lead to a systemic inflammation. It is worthy to note that the biological response is similar in our study to the response reported in the study in patients with femoral access<sup>[7]</sup>. In all these patients, a venous catheter is mandatory. This could by itself induce a biological answer. This hypothesis deserves to be investigated. Second, the manipulation of the guidewires and catheters could lead to minor but significant endothelial injury in normal arteries as well as destabilization of instable atheroma plaques.

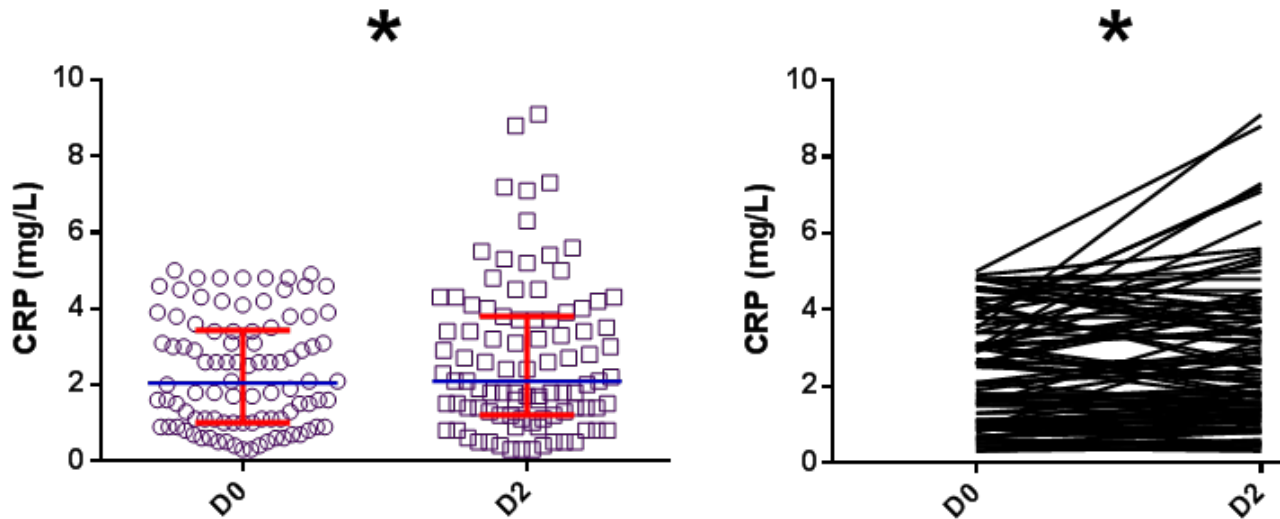


Figure 2 Variation of CRP level between baseline and D2.

Third, many confounders have to be taken into account, such as the contrast agents, the drugs used during the procedure, able of endothelial injury or by contrast endothelial protection (antioxidative properties).

Clinical significance is nevertheless not established. Indeed, even if biological inflammation occurs statistically significantly, with an increase of 17%, it does not mean clinical consequences. Probably biological inflammatory variations can occur in various clinical conditions for instance even in case of physical activity<sup>[17]</sup>. On the other hand, basal level of CRP has been proposed as a player in vasospasm<sup>[18]</sup> or more importantly in stratification in various pathophysiological conditions<sup>[19]</sup> including patients with coronary plaques<sup>[20]</sup>. This does not deal with evolution of CRP levels after coronary angiogram. Furthermore, CRP has been established to vary in patients independently of the severity of coronary artery disease<sup>[21]</sup>.

Further prospective studies could be of interest, in order to evaluate concomitantly the biological inflammatory answer as well as endothelial function<sup>[22]</sup>, reactive oxygen species, etc. More importantly many perprocedural protection attitudes can be proposed for cardioprotection or nephroprotection. Such proposals could also offer “systemic” protection by reducing oxidative stress or systemic inflammatory response that could appear as a new surrogate endpoint in studies on perprocedural organ protection. For instance, remote conditioning is currently proposed for nephroprotection<sup>[23,24]</sup> or ongoing studies (for instance NCT02463604). Based on pathophysiological approach, it could also logically reduce systemic response.

#### Limits

The study is retrospective and the patients with CRP available at day 0 and day 2 have been included, hence an information bias. However, for ethical reasons, the design adopted here seems the most appropriate to us. For similar reasons, the assessment of the biomarkers in the following days seems not reasonable.

Only the CRP has been assessed although many inflammatory biomarkers could be proposed in studies, including the proinflammatory cytokines (such as IL-1, IL-6, TNF-alpha), other cytokines, procalcitonin, activated cells and so on. Nevertheless, CRP is considered as the gold-standard for the assessment of biological inflammatory response and is routinely used as its significance is obvious for clinicians, by contrast with the other biomarkers.

## CONCLUSION AND PERSPECTIVES

The take-home messages are (1) in patients undergoing PCI, there's a small systemic inflammatory response as detectable by CRP; (2) the clinical significance is unknown; (3) the rate of return of CRP to baseline is unknown in this study; (4) other inflammatory markers may also be elevated, and remain to be explored in this clinical setting. This has to be taken into consideration especially in clinical trials targeting inflammation.

## CONFLICT OF INTEREST

There are no conflicts of interest with regard to the present study.

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