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Endothelial function after ST-elevation myocardial infarction in patients with high levels of high-sensitivity CRP and Lp-PLA$_2$: A substudy of the RESPONSE randomized trial☆,☆☆

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ABSTRACT

Background: The combination of high levels of high-sensitive C-reactive protein (hs-CRP) and lipoprotein-associated phospholipase-A$_2$ (Lp-PLA$_2$) was recently shown to correlate with increased cardiovascular risk. Endothelial dysfunction is also known to be a risk factor for cardiovascular events.
Aim: To test among patients with previous ST-elevation myocardial infarction (STEMI) the hypothesis that high levels of both hs-CRP and Lp-PLA$_2$ may be associated with impaired endothelium-dependent vasodilatation.
Methods: In this substudy of the RESPONSE randomized trial, we used reactive hyperemia peripheral artery tonometry (RH-PAT) 4 to 6 weeks after STEMI and primary percutaneous coronary intervention (PPCI) to non-invasively assess endothelial function (RH-PAT index <1.67 identified endothelial dysfunction). Reliable measurements of RH-PAT, hs-CRP, and Lp-PLA$_2$ were obtained in 68 patients, who were classified as high-risk if levels of both hs-CRP and Lp-PLA$_2$ were in the upper tertile (≥3.84 mg/L and >239 μg/L, respectively).
Results: Patients were 57.4 ± 9.7 years and 53 (77.9%) were men. 11 (16%) patients were classified as high-risk and 57 (84%) as low-to-intermediate-risk. The RH-PAT index was 1.68 ± 0.22 in high-risk and 1.95 ± 0.63 in low-to-intermediate-risk patients ($p = 0.17$). Endothelial dysfunction was present in 8 (72.7%) high-risk and 26 (45.6%) low-to-intermediate-risk patients ($p = 0.09$). Framingham risk score, NT-proBNP and fibrinogen levels were higher in high-risk patients ($p \leq 0.03$).
Conclusion: In this population of patients with recent STEMI and PPCI, we observed between patients with high hs-CRP and Lp-PLA levels and all other patients no more than numerical differences in endothelial function that did not reach a statistical significance. Nevertheless, further research in larger study populations may be warranted.

1. Introduction

While common cardiovascular risk factors at best provide a reasonable prediction of cardiovascular events [1], the addition of biomarkers of systemic inflammation, such as high-sensitive C-reactive protein (hs-CRP), can improve risk prediction [2]. A recently published study showed that an aggregate risk score including hs-CRP greatly enhanced the risk prediction of death and myocardial infarction in patients with suspected or known coronary artery disease [4]. In addition, lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$), a specific marker for vascular inflammation, was found to predict future cardiovascular events independently of hs-CRP [5–7], suggesting an additive role for risk prediction. This is supported by the fact that in a population-based study, the combination of elevated levels of hs-CRP and Lp-PLA$_2$ correlated with increased cardiovascular risk [8].

Abbreviations: hs-CRP, high-sensitive C-reactive protein; Lp-PLA2, lipoprotein-associated phospholipase A$_2$; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; RH-PAT, reactive hyperemia peripheral artery tonometry; STEMI, ST-elevation myocardial infarction.

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Patients who survive an ST-elevation myocardial infarction (STEMI) are at high risk of future recurrent cardiovascular events [9]. Within this patient population, the combination of elevated levels of hs-CRP and Lp-PLA_2 might be able to identify subjects with a particularly high risk. As endothelial dysfunction (i.e. impaired endothelium-dependent arterial vasodilatation) is known to be an independent risk factor of future cardiovascular events [10,11], we tested in a local substudy of the RESPONSE (Randomised Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists) trial [14] the hypothesis that elevated levels of both hs-CRP and Lp-PLA_2 may be associated with reduced endothelial function in patients with recent STEMI.

2. Methods

2.1. Study population and study design

This prospective cohort study was performed in STEMI patients of the RESPONSE trial [12], who underwent treatment by PPCI for acute STEMI (≤12 h after symptom onset) and non-invasive assessment of endothelial function with the RH-PAT method after 4 to 6 weeks at Thoraxcentrum Twente in Enschede. PPCIs were performed between October 2007 and December 2008. Of a total of 75 RESPONSE trial participants at Thoraxcentrum Twente, who were treated for STEMI and underwent RH-PAT measurements, 71 had analyzable RH-PAT registrations and 68 patients had laboratory measurements of hs-CRP and LpPLA2. This resulted in a study population of 68 patients.

Details of the randomized RESPONSE trial have previously been reported [12]. In brief, patients had to be 18 to 80 years, without surgery or additional PCI being planned within 8 weeks from PPCI, without congestive heart failure New York Heart Association (NYHA) class III or IV, and with a life expectancy of at least 2 years.

As inflammation and repair processes of the infarcted myocardium might have disturbed endothelial function measurements during the first weeks after the STEMI and endothelial dysfunction had not been fully recovered under medication, endothelial function was assessed 4 to 6 weeks after the PPCI [13–15]. All patients were seen in the outpatient clinic and the research department of Thoraxcentrum Twente, where non-invasive assessment of the endothelial function was performed according to strict rules in a dedicated laboratory [16].

All patients provided written informed consent for both participation in the RESPONSE multicenter trial and the present single-center substudy. Trial and substudy complied with the Declaration of Helsinki for investigation in human beings and were approved by accredited Medical Ethical Committees in Amsterdam and Twente, the Netherlands.

2.2. Patient characteristics and follow-up

The following information was collected through interviews during visits in our outpatient clinic 4 to 6 weeks after STEMI: age; sex; body mass index (kg/m^2); arterial hypertension (blood pressure >140/90 mmHg or treatment with anti-hypertensive medication); history of smoking (previous or current smoker); history of previous myocardial infarction or percutaneous coronary intervention (PCI); presence of diabetes mellitus (patient history and/or treatment with insulin or oral anti-glycemic agents); and history of hyperlipidemia or treatment with lipid-lowering drugs. The Framingham Risk Score (10-year risk prediction for fatal and non-fatal coronary heart disease) was determined to sketch a patient risk profile.

2.3. Laboratory assessment of the biochemical markers

Venous blood samples were drawn after a minimum of 8 h of fasting. The laboratory markers total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, hemoglobin A1c, creatinine, fibrinogen, apolipoprotein A1 & B100, troponin I and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were assessed according to manufacturer instructions. After centrifugation, plasma and serum aliquots were stored at −80 °C. A commercially available Lp-PLA_2 enzyme-linked immunosorbent assay kit (third generation PLAC™ Test; diaDexus Inc., South San Francisco, CA) was used to determine the lipoprotein-associated phospholipase A_2 mass. The inter-assay precision was determined by measuring two controls of known concentration (low and high) in 10 separate assays. The coefficient of variation on all 10 plates was 7% and 6%, respectively. The hs-CRP concentrations were determined by nephelometry using a BN ProSpec® system (Siemens). The detection limit was 0.23 mg/L and the mean inter-assay coefficient of variation was 2.8%.

The thresholds of the hs-CRP tertiles were determined at 1.03 mg/L and 3.84 mg/L; the thresholds of the Lp-PLA_2 tertiles were 190 μg/L and 239 μg/L comparable to AHA/CDC guidelines [17] and ARIC study [8].

2.4. Assessment of endothelial function

Endothelial function was evaluated with the RH-PAT method. The finger pulse wave amplitude was assessed with the EndoPAT-2000 sensing device and finger plethysmographic probes (Itamar Medical, Caesarea, Israel), both at baseline and during ischemia-induced hyperemia. All measurements were performed in the early morning in a dedicated laboratory after fasting for at least 8 h. Patients also had to refrain from caffeine consumption, smoking, and vasoactive medications. At least 15 min prior to testing, blood pressure was measured and a blood sample was drawn in the control arm. Before any measurement, patients had an acclimatization period of 20 min in a quiet room, lying in a hospital bed at an ambient temperature of 21 to 23 °C.

The RH-PAT method has previously been reported in detail [18-20]. In brief, measurements were performed by the use of probes on index fingers of both the study and control arm. Baseline measurements were recorded for 5 min prior to inducing ischemia by inflating a blood pressure cuff on the upper arm of the study arm for 5 min to supra-systolic pressures. This led to NO release from functional endothelium and thus vasodilatation, which was recorded by the sensors in the finger cuff through beat-to-beat finger pulse wave analysis [19,21]. Following the release of the blood pressure cuff, the ratio of the pulse amplitude of the hyperemic finger and the baseline amplitude was calculated. Subsequently, that ratio was divided by the corresponding ratio, obtained in the control arm, to calculate the RH-PAT index (high values indicate good endothelial function) [19,21]. Hamburg et al. demonstrated that the maximum hyperemic response can be expected 90 to 120 s after cuff deflation [20]. Therefore, in the present study, the reactive RH-PAT index was calculated as the ratio of the mean hyperemic pulse wave analysis over a period of 30 s, beginning at 90 s after cuff deflation, divided by the baseline pulse wave analysis (mean baseline measurements for 3.5 min), and normalized to the concurrent measurements of the control arm. Based on previously reported data, endothelial function was divided into two groups: endothelial dysfunction (RH-PAT <1.67) and normal endothelial function (RH-PAT ≥1.67) [21].

2.5. Statistical analysis

Data are presented as frequencies (%) or mean ± standard deviation (SD). We used the Fisher's exact chi-square test for categorical variables and the T-test for continuous variables to compare patients with high risk versus patients with low-to-intermediate risk. A p-value <0.05 was considered statistically significant. Analyses were performed with SPSS (version 21.0).

3. Results

3.1. Characteristics of the study population

Demographics and clinical characteristics of the 68 patients of the study population are presented in Table 1. Overall, patients were 57.4 ± 9.7 years and predominantly men (n = 53, 77.9%).

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